DISSERTATION TITLED

"PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS AND ITS CORRELATION WITH OTHER MICROVASCULAR COMPLICATIONS"

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CERTIFICATE

This is to certify that the dissertation entitled **"PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS AND ITS CORRELATION WITH OTHER MICROVASCULAR COMPLICATIONS"** is a bonafide work done by **DR. PUSHPA MASIWAL**, Post Graduate Student, Institute of Internal Medicine, Madras Medical College, Chennai-3, in partial fulfillment of the University Rules and Regulations for the award of MD Branch – I General Medicine, under our guidance and supervision, during the academic year 2012 - 2015.

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DECLARATION

I solemnly declare that the dissertation entitled **"PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS AND ITS CORRELATION WITH OTHER MICROVASCULAR COMPLICATIONS"** is done by me at Madras Medical College, Chennai-3 during January 2014 to June 2014 under the guidance and supervision of Prof. K.S.CHENTHIL, M.D., to be submitted to The Tamilnadu Dr. M.G.R Medical University towards the partial fulfillment of requirements for the award of M.D. DEGREE IN GENERAL MEDICINE BRANCH-I.

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ABBREVIATIONS

ANS	Autonomic nervous system
ARI	Aldose Reductase Inhibitors
AGE	Advanced Glycation Endproducts
BP	Blood Pressure
CAN	Cardiac Autonomic Neuropathy.
DA	Diabetic Amyotrophy
DAN	Diabetic Nutonomic Neuropathy
DCCT	Diabetes Control and Complications Trial
EMG	Electromyography
ECG	Electrocardiography
GFR	Glomerular Filtration Rate
NO	Nitric Oxide
NCS	Nerve Conduction Studies
OHA	Oral Hypoglycaemic Agents
PCR	Protein Creatinine Ratio
PKC	ProteinKinase C
RFT	Renal Function Test
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TCA	Tricyclic Antidepressants

CONTENTS

ABSTRACT

Investigator: Dr Pushpa Masiwal, Prof. Dr K S Chenthil.

Background: The presence of cardiac autonomic neuropathy (CAN) in patients with type 2 diabetes mellitus (T2DM) is associated with chronic micro vascular complications and increased mortality.

Objective: To assess the prevalence of CAN in T2DM and to investigate any possible association between CAN and micro vascular complications.

Method: In this observational study, patients underwent laboratory investigations, biothesiometry, fundus examination, and CAN assessment by CANS analyser.

Results: The prevalence of CAN dysfunction was found to be 80.39% according to our study. CAN was found to be significantly associated with age of patients, diabetic neuropathy and diabetic retinopathy.

Conclusion: CANS dysfunction appears much before patients manifest signs and symptoms of this condition and it is correlated with other micro vascular complications.

Keywords: Type 2 Diabetes Mellitus, Cardiac Autonomic Neuropathy, Micro vascular Complications.

INTRODUCTION

One of the most overlooked and serious complications of the most common and dreaded non communicable disease Diabetes Mellitus is cardiac autonomic neuropathy.

Information regarding the frequency of cardiac autonomic neuropathy in diabetic population is limited. It has poor prognosis and at times presents with orthostasis, exercise intolerance, postural hypotension, enhanced intra-operative and peri-operative cardiovascular instability and increased incidence of silent myocardial infarction and ischemia and sudden death.

This could be due to functional abnormality or structural damage to various components of ANS. Systemic hypertension, distal symmetrical peripheral neuropathy, retinopathy and persistent poor glycemic status are in general major risk factors in the development of cardiac autonomic neuropathy in both Type 1and Type 2 Diabetes Mellitus.

This study aims to assess the prevalence of CAN among the patients of T2DM of varying duration and correlate any possible influences of age, duration of diabetes, hypertension, coexistent peripheral neuropathy, nephropathy and/or retinopathy on occurrence of cardiac autonomic neuropathy.

AIMS AND OBJECTIVES

To study the prevalence of CAN in T2DM in south Indian population.

To correlate the prevalence of cardiac autonomic neuropathy in Type 2 Diabetes Mellitus with duration of disease, severity and other microvascular complication.

REVIEW OF LITERATURE

Diabetes Mellitus is a group of metabolic disorders with hyperglycaemia as a common phenotype. It is a chronic and complex illness which requires regular medical care beyond glycaemic control.

Diabetes has been classified into different types according to the etiopathogenesis.

The latest classification as given in ADA2014 publication is included here.

Diabetes can be classified into four clinical categories:

- Type 1 diabetes (due to β-cell destruction, usually leading to absolute insulin deficiency)
- Type 2 diabetes (due to a progressive insulin secretory defect on the background of insulin resistance)
- Other specific types of diabetes due to other causes, e.g., genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of HIV/ AIDS or after organ transplantation)
- Gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy that is not clearly overt diabetes)

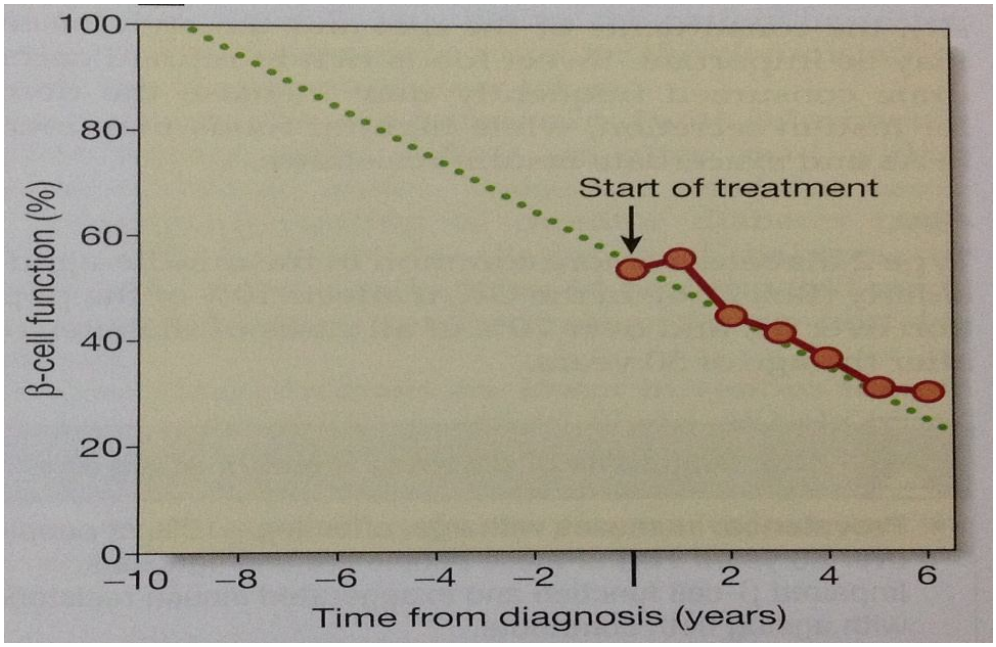
Some patients cannot be clearly classified as type 1 or type 2 diabetic.

DIAGNOSIS OF DIABETES

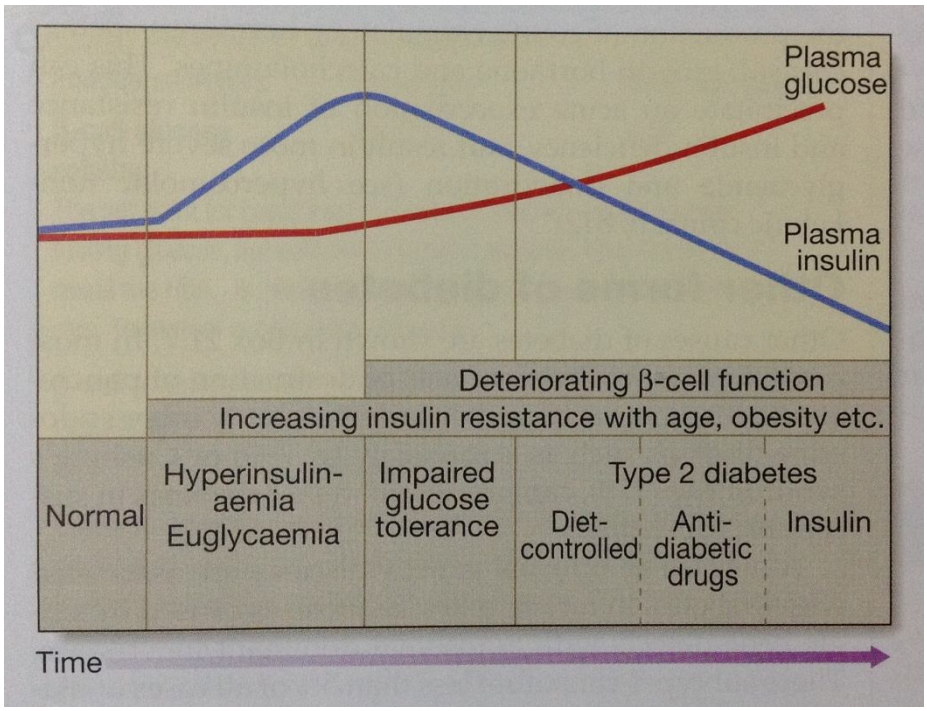
As per ADA 2014 guidelines

A1C ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
Two-hour PG ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).
*In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.

TYPE 2 DM NATURAL HISTORY



TYPE2 DM NATURAL HISTORY

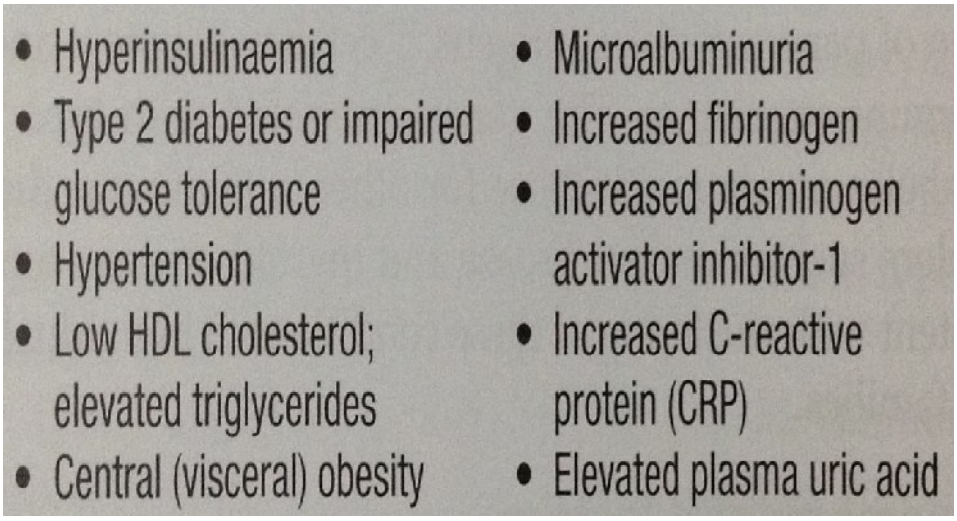


PATHOGENESIS

It is complex due to varying combination of insulin resistance and relative insulin deficiency.

INSULIN RESISTANCE

T2DM is often associated with visceral obesity, dyslipidaemia and hypertension and is called insulin resistance syndrome



Central obesity is the most important factor in insulin resistance. The above mentioned cluster of conditions predispose to cardiovascular disease. What is the main cause of insulin resistance is still unclear. The metabolically active central adipose tissue (intra-abdominal) releases free fatty acids which in the peripheral tissue compete with glucose for oxidation which in turn induces insulin resistance[4].

Hormones like adipokines, which are released form adipose tissue act on specific receptors to influence sensitivity in various tissues. Another important determinant of insulin sensitivity is physical activity.

Physical inactivity causes down regulation of insulin sensitive kinases which cause accumulation of free fatty acids within skeletal muscles. Therefore sedentary people with same BMI are more insulin resistant than active people[3].

Fat deposition in the liver is often associated with central obesity and is exacerbated by insulin resistance. Most people with T2DM have fatty infiltration of liver which may improve with effective treatment of diabetes and dyslipidaemia.

RELATIVE INSULIN DEFICIENCY (Pancreatic Beta Cell Failure):

At the time diabetes is diagnosed in an individual, about 50% of beta cell mass of pancreas is already lost. The most important pathological change of T2DM is deposition of amyloid around pancreatic beta cells. Added on to this, elevated blood sugar levels and free fatty acids exert a toxic effect on pancreatic beta cells further impairing insulin secretion. The alpha cell mass remains unchanged leading to increased glucagon secretion which contributes to hypoglycaemia.

GENETIC PREDISPOSITION

Various studies have shown the concordance rates for T2DM among monozygotic twins is around 100%. Apart from genetic involvement development of diabetes is influenced by strong environmental factors.

Over 20 genes have been identified to be associated with T2DM. The genetic variation in TCF7L2 exerts a large effect in development of T2DM. 10% of the population having 2 copies of this high risk variant have 2 fold increased risk of development of T2DM.[2]

ENVIRONMENTAL AND OTHER RISK FACTORS

Diet and Obesity:

Over eating combined with obesity and under activity are associated with increased incidence of T2DM. There is a tenfold increase in T2DM in people with Body Mass Index more than $30 kg/m^2$. Obesity is a diabetogenic factor in genetically predisposed individuals. Foods rich in carbohydrates increase demand for insulin secretion, and fatty foods increase insulin resistance

Age

T2DM is common in middle age and elderly people. Recent studies in India have shown increased incidence of T2DM in adolescent age group, this is due to poor dietary habits, sedentary lifestyle and obesity.

Pregnancy

Pregnancy by itself is an insulin resistant state where the pancreatic beta cells are not able to meet the increased insulin demands in pregnancy. This is due to the placental hormones which affects the glucose tolerance in pregnancy.

COMPLICATIONS OF DIABETES MELLITUS

MICROVASCULAR COMPLICATIONS

Diabetic Retinopathy

It is the most common micro-vascular complications leading to blindness in diabetes. Early diagnosis by annual fundus examination is mandatory in all diabetic individuals.

Hypoglycaemia per se increases retinal blood flow and vasoactive substances production increases. There is endothelial cell proliferation which causes closure of capillaries. Long term hypoxia increases the production of vascular endothelial growth factor (VEGF) leading to endothelial cell proliferation and increased vascular permeability.[30]

Modifiable Risk Factors

- Hyperglycaemia
- Hypertension
- Dyslipidaemia
- Smoking

Non Modifiable Risk Factors

- Duration of diabetes
- Age
- Genetic predisposition
- Ethnicity

Pathophysiological Events in Diabetic Retinopathy

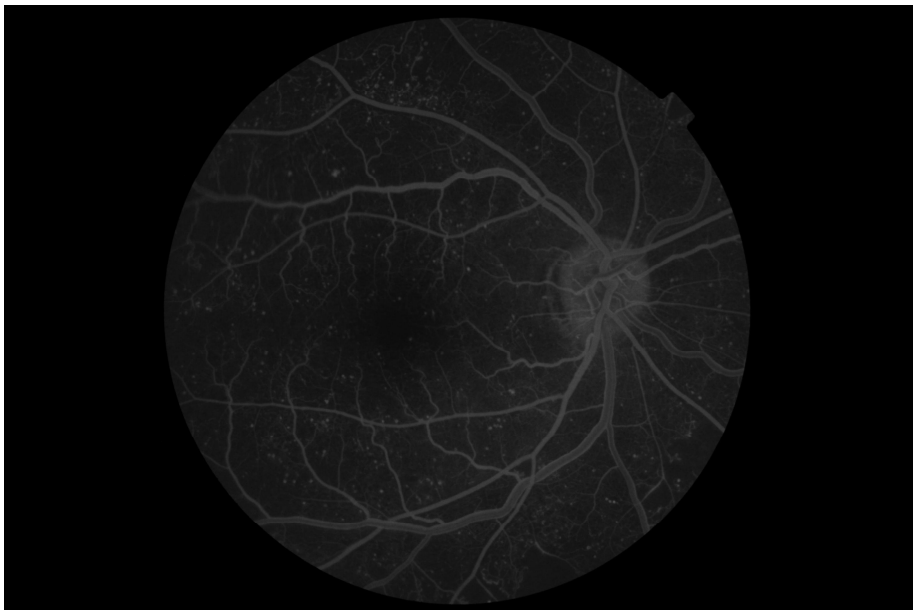
- Basement membrane thickening
- Pericyte loss
- Increased capillary permeability
- Microaneurysms
- Smooth muscle death
- Capillary weakening
- Reduced retinal blood flow

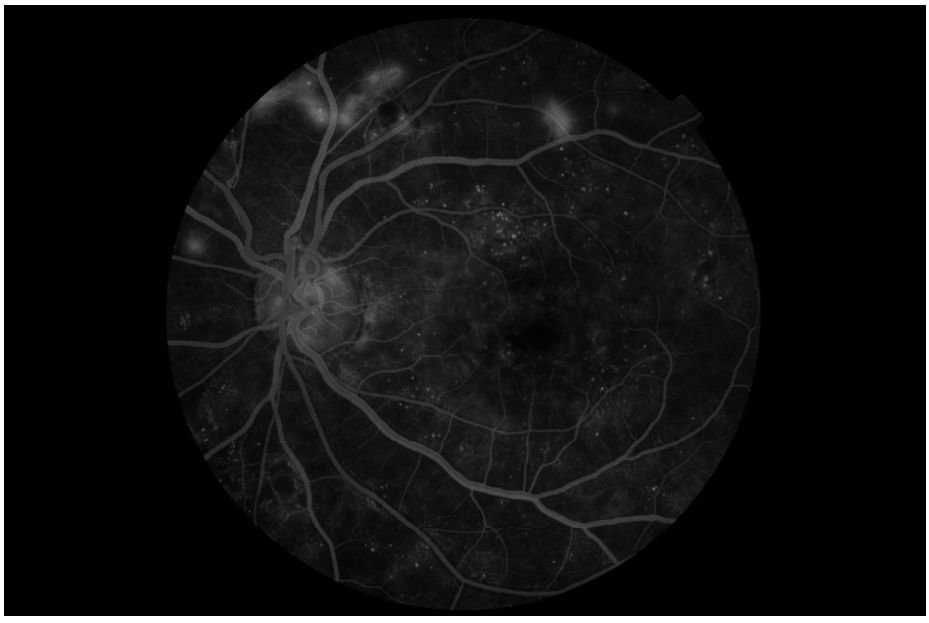
CLINICAL FEATURES OF DIABETIC RETINOPATHY

- Microaneurysms
- Retinal haemorrhages (blot and dot)
- Exudates
- Cotton wool spots
- Venous changes
- Neovascularisation (retina and iris)
- Pre-retinal/subhyaloid haemorrhages
- Vitreous haemorrhages
- Fibrosis/gliosis
- Diabetic maculopathy

SEVERE NON PROLIFERATIVE DIABETIC RETINOPATHY

FUNDUS FLOURESEIN ANGIOGRAPHY





Investigative Techniques for Diabetic Retinopathy:

- Digital colour retinal photography
- Fundus fluorescein angiography
- Optical coherence tomography
- Ultrasound B scan examination
- Perimetry

Screening for Diabetic Retinopathy

Universal screening for diabetic retinopathy is mandatory for all diabetic individuals. Fundus examination using ophthalmoscope is the screening procedure in clinical setup. Incidence of diabetic retinopathy increases with increasing duration of diabetes, for T2DM screening starts at the time of diagnosis whereas for T1DM it usually starts after 5 years of diagnosis.

Treatment of Diabetic Retinopathy

- Laser photocoagulation
- Vascular endothelial growth factor inhibitors like Bevacizumab and Ranibizumab
- Vitrectomy

POST – PAN RETINAL PHOTO COAGULATION

DIABETIC NEPHROPATHY

Around 40 % of diabetic individuals are affected by Diabetic Nephropathy. It is the most frequent reason for kidney disease in patient undergoing renal replacement therapy. It is characterised by slowly increasing urinary albumen excretion over the years accompanied by gradually rising blood pressure and a fall in GFR.[24]

Once diabetic nephropathy sets in, there is an increased risk in the diabetic patient to develop other micro vascular as well as macro vascular complications of diabetes. Leading cause of death in Diabetic nephropathy is from cardiovascular diseases. Clinically Diabetic nephropathy occurs in two stages, viz: microalbuminuria and macroalbuminuria.

RISK FACTORS OF DIABETIC NEPHROPATHY

Modifiable

- Hyperglycemia
- High Blood Pressure
- Dyslipidemia
- Smoking
- Increased protein intake

Non- Modifiable

- Duration of Diabetes
- Genetic Predispotion

PATHOGENESIS OF DIABETIC NEPHROPATHY

Classic Glomerulosclerosis is characterized by

- Glomerular basement membrane thicknening
- Diffuse mesangial sclerosis
- Hyalinosis
- Microaneurysms
- Hyaline arteriosclerosis

SCREENING TEST FOR DIABETIC NEPHROPATHY

- Spot albumin – creatinine ratio
- 24 hrs urinary protein and creatinine and creatine clearance
- Urinary protein in timed (4 hrs) or overnight collection

Since there is day –to-day variability in albumin excreation atleast 2 of 3 collections done in 3-6 month period must be elevated.

Screening for Diabetic Nephropathy in T1DM begins 5 yrs after diagnosis but poor glycemic control in the first 1 yr of diagnosis screening starts after 1 yr and yearly thereafter.In T2DM screening starts at time of diagnosis and yearly follow up is necessary.

TREATMENT OF DIABETIC NEPHROPATHY

- Strict glycemic control
- Blood pressure control
- Avoiding nephrotoxic drugs
- Dialysis
- Renal transplantation

DIABETIC NEUROPATHY

Diabetic neuropathy is fairly common complication in diabetes. Neuropathy clinically manifests as numbness of feet which results in ulceration and infection, neuropathic pain which can be severe and disabling, and autonomic neuropathy which can involve several systems. Prevalence rates of diabetic polyneuropathy is approximately 30% among diabetic population.

The prevalence of neuropathy is associated with increasing age, poor glycaemic status and longer duration of the disease.[1] Neuropathy is often associated other microvascular complications. Increasing height and cardiovascular risk factors (cigarette smoking, hypertension, hyperlipidaemia) also associated with increased prevalence of neuropathy. The type of diabetes does not appear to influence its prevalence.

The onset and triggers for diabetic neuropathy are not very clear. They are the cause of pain, distress, suffering and poor quality of life. If not taken care of in the early stages, this neuropathy can lead to foot ulceration. Charcot's neuroarthropathy may develop and patient with

improper care and control can undergo amputations which is actually a potentially preventable condition.[6]

DEFINITION

The simplest definition of Diabetic Neuropathy is: "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes" (Boulton AJM, Jervell J: 1997).

PATHOGENESIS

The DCCT results have demonstrated a significant decrease in development and progression of symptomatic neuropathy (64%). Asymptomatic neuropathy which is detected by nerve conduction studies (44%), and also autonomic dysfunction which is about 53% in T1DM individuals with optimal glycemic control.

Similarly symptomatic and asymptomatic neuropathy develops and progresses gradually over years and is related to both hyperglycemia and hypoinsulinemia in type 2 diabetic patients.

Hyperglycaemia sets in a complex chain of events which include polyol pathway activation, depletion of myoinositol, reduction in PKC activity and a decrease in activity of nerve Na+ , K+ -ATPase. These

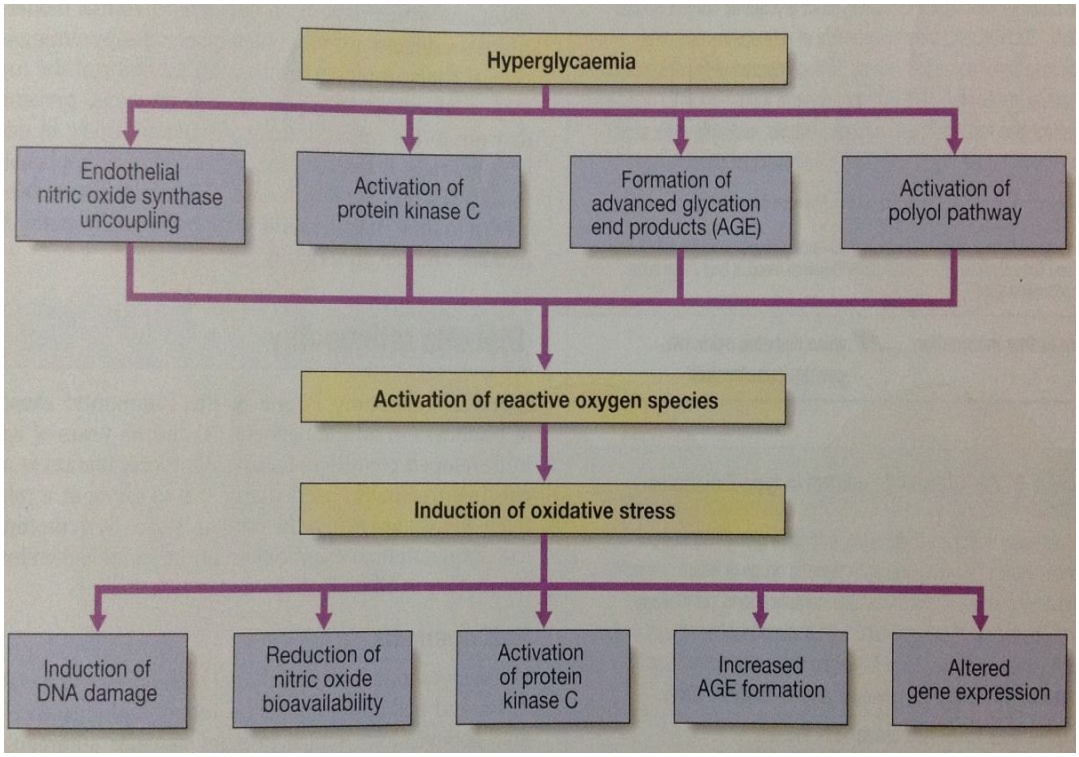
changes are implicated in the development of a reduction in nerve conduction velocity.

The characteristic feature of distal symmetrical neuropathy is distal axonal loss, which is associated with an exclusive ‘dying back’ phenomenon. Myelinated fibre density is reduced. It is difficult to assess small unmyelinated fibres which contribute upto 80% of nerve fibres

Diabetic peripheral nerve injury- possible hypothesis:

- Nerve microvascular dysfunction
- Polyol pathway hyperactivity
- Protein kinase C hyperactivity
- Non-enzymatic glycation
- Increased free radical formation
- Abnormalities of nerve growth factors

PATHOGENESIS OF DIABETIC NEUROPATHY

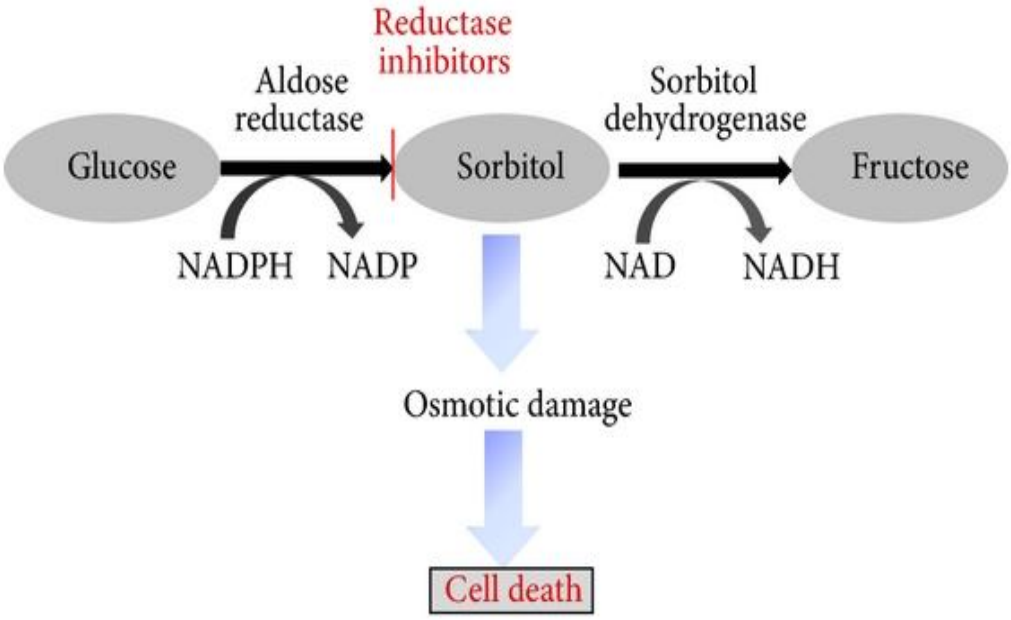


POLYOL PATHWAY HYPERACTIVITY

Glucose is normally converted by the action of enzyme hexokinase into glucose -6-phosphate. When there is hyperglycaemia this excess glucose is first reduced to sorbitol by the action of another enzyme aldose reductase. The sorbitol so formed, then changes to fructose under the influence of sorbitol dehydrogenase.

The elevated sorbitol levels in diabetic nerves is associated with depletion of myoinositol and also a decrease in Na+ -K+ -ATPase which is necessary for exchange of intracellular as well as extracellular sodium and there by nerve membrane potential. ARI's help in improvement in nerve conduction velocity.

THE POLYOL PATHWAY



NON-ENZYMATIC GLYCATION

Non-enzymatic glycosylation of proteins is a feature of diabetes and is a initiating factor for nerve demyelination associated with interference of axonal transport. AGE absorb NO leads to reduction in blood flow to the nerves. Aminoguanidine, an avid inhibitor of AGE formation improves deficits in nerve conduction.

OXIDATIVE STRESS

Increased free radical generation due to non-enzymatic glycation and increased activity of polyol pathway leads to NADH depletion. Hence the nerve function is impaired by oxidative stress compounded by its toxic effects and by decreased NO and reduced blood supply to the nerves

NEUROTROPHIC FACTORS

Experimental diabetes shows reduction in growth factor eg: I,II and neurotrophin family. Treatment with nerve growth factor improves sensory neuropathy caused by dysfunction of small fibre.

ACTIVATION OF PROTEIN KINASE C

Increased activity causes increase in synthesis of diacylglycerol (DAG) which leads to abnormalities in the vascular function. Treatment with PKC inhibitor corrects deficits in the retinal perfusion and prevents early glomerular hyperfiltration and increases in urinary albumin excretion among the diabetic rats and it has also shown to improve nerve conduction velocity, improve perfusion deficits and may even protect endothelial relaxation.

MICROVASCULAR FACTORS

Thickening of basement membrane of endoneural capillaries, pericytes degeneration, hyperplasia, and the swelling of the endothelial cells and at times blood vessel blockage are some common microvascular changes that can be seen in nerves. Impairment of blood flow to nerves can cause a reduction in endoneural oxygenation.

To summarize, a lot of metabolic abnormalities are brought about by the diabetic state as mentioned above which have a negative impact on nerve perfusion but the vascular endothelium is the major target.

Activation of the PKC system, oxidation stress and non-enzymatic glycation and decreased neurotrophic factors cause reduction in nerve NO.

Endoneural capillary occlusion and the haemorrhagic abnormalities which are associated with diabetes can further worsen the blood flow to the nerves causing hypoxia and thus lead to structural and also functional abnormalities in the nerves.

CLASSIFICATION OF DIABETIC NEUROPATHY

Neuropathy is classified according to clinical presentation. Various classifications are available but the commonly used one is as follows

1.Chronic, progressive distal symmetric polyneuropathy

- Mixed sensorimotor
- Predominantly sensory
- Predominantly autonomic

2. Acute axonal polyneuropathy

- acute, painful, weight loss, poor control (cachexic)
- acute, painful, weight gain, good control (insulin neuritis)

3. Proximal motor neuropathy (Amyotrophy)

4. Mononeuropathies

- mononeuropathy multiplex
- cranial
- truncal

5. Entrapment neuropathies

CHRONIC SENSORY MOTOR NEUROPATHY (CHRONIC DISTAL SYMMETRICAL NEUROPATHY)

It is the most common neuropathic syndrome which often affect more than 80% of patients with neuropathic symptoms. It's a diffuse and symmetrical disorder which usually affects the lower limbs in stocking fashion, involvement of the hands in a glove pattern being rare. The pattern of sensory loss is length-related.

Most patients with chronic sensory motor neuropathy will have an autonomic component which is often sub-clinical and detected only by formal testing. As the disease advances, it becomes a sensory motor neuropathy, although significant motor involvement is uncommon early in the natural history of the disease. The onset is gradual and progresses with increasing duration of diabetes.

The incidence of chronic sensory motor neuropathy appears to be related to poor glycaemic control. While autonomic dysfunction is common, symptoms of autonomic neuropathy are rare. Abnormal cardiovascular tests have been reported in 16-40% of diabetic subjects.

AUTONOMIC NEUROPATHY

Diabetes is a major cause of autonomic nervous system dysfunction. Autonomic dysfunction is common in patients with longstanding diabetes increasing age, poor glycaemic status and presence of risk factor related to cardiovascular system.

It is one of the least understood and recognized complication of diabetes and has a very significant impact on quality of life and survival in individual who suffer with diabetes. [2] The disorders of metabolism in diabetes lead to a widespread and diffuse damage of small and large vessels, peripheral nerves and autonomic nerves.

Involvement of ANS can damage cardiovascular, neurovascular , gastrointestinal and genitor-urinary systems and also impair certain metabolic functions like glucose counter-regulations. Autonomic neuropathy sets in gradually and it also progresses slowly.

The prevalence of DAN will depend on the population which is studied and also the amount of tests for detection of autonomic function that are employed.

In EURODIAB study, autonomic neuropathy prevalence was defined as presence of at least two abnormal CAN function tests.

Diabetic autonomic neuropathy (DAN) is often associated with diabetic predominantly sensory neuropathy. It is frequently under diagnosed on a clinical basis. The severity of autonomic dysfunction ranges from asymptomatic to severe disability.

Common manifestations are pupillary size and reduction of light responses, episodic nocturnal diarrhea, constipation and gastric atony, orthostatic hypotension, dizziness, resting tachycardia, cardiac arrhythmia, and silent myocardial infarction. Genitourinary system dysfunction presents with bladder atonia, distention, recurrent infection, and impotence.[17]

DAN is seen frequently in T1DM, and the incidence seems to increase with increasing age and longer duration of renal disease. Furthermore, patients suffering with DAN have a much increased risk of development of renal infections and unexplained cardiorespiratory arrest, with a higher mortality rate.

ORGANISATION OF ANS

The ANS organisation and physiological control relies on its division into sympathetic and parasympathetic nervous system. Fight and flight is an important physiological response which is mediated by sympathetic stimulation and is manifest by increased heart rate , increased BP, energy store mobilisation and alertness.

Epinephrine, nor-epinephrine and dopamine are the major neurotransmitters which mediate the cellular responses by some interaction with special G- protein coupled adrenergic receptors namely α1 ,α2& β1 ,β2 ,β3 and dopaminergic receptors namely D1 ,D2&D3. On the contrary, parasympathetic stimulation usually produces effects which are opposite to effects produced by stimulation of sympathetic nervous system .eg: decreased heart rate , decrease in cardiac contractility and increase of digestive function.

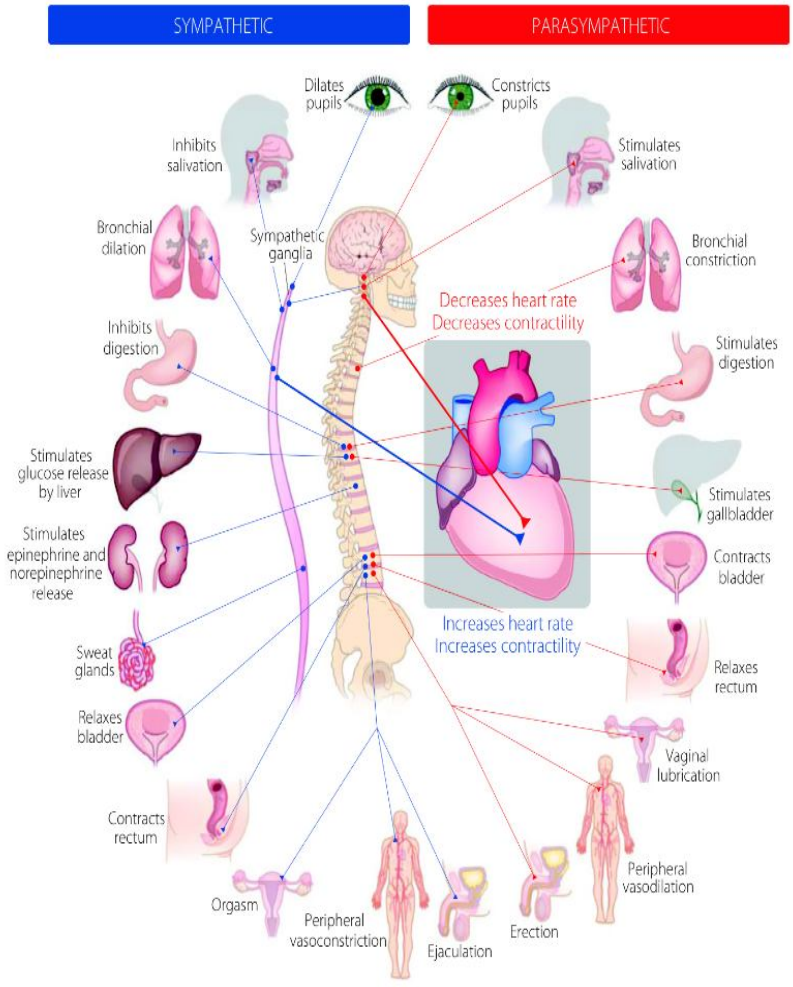
Acetylcholine which is the major neurotransmitter in this system interacts with its muscaranic receptors which are G protein couples namely M 1-M5 and also with nicotinc receptors i.e neuronal I – III ,muscle type IV.

Parasympathetic neurons are situated in brain stem medulla and also in the sacral region of one's spinal cord. Sympathetic neurons reside in the thoracolumbar spinal cord.

Cranial nerves and also spinal nerves are helpful in projecting the pre synaptic myelinated axons to synapses located with in ganglia and from here the post synaptic unmyelinated fibres arise, which reach the innervated organ.

Although these two systems apparently have opposite actions, a well coordinated firing by both is necessary. Physiological functions of ANS have been depicted in the following figure.

FUNCTIONS OF ANS



CLINICAL MANIFESTATIONS OF AUTONOMIC NEUROPATHY

Cardiovascular

- Resting tachycardia
- Heart rate abnormalities
- Oedema
- Postural hypotension
- Arrhythmia
- Sudden death

Dermatological

- Gustatory sweating
- Dry skin
- Sudomotor dysfunction
- Arterio-venous shunting

Neurological

- Pupillary dysfunction

Gastrointestinal

- Gastroparesis
- Diarrhoea
- Constipation

Genitourinary

- Erectile dysfunction
- Retrograde ejaculation
- Atonic bladder
- Bladder infection
- Abnormal renal sodium handling

Respiratory

- Bronchoconstrictor dysfunction

CARDIOVASCULAR AUTONOMIC NEUROPATHY

Where there is damage of autonomic fibres which innervate heart and its blood vessels, it causes certain abnormalities not only of heart rate control but also vascular dynamics. Technological advances in the past decade have made it possible to identify autonomic dysfunction in early stages with the help of objective standardised measures. This allows intervention earlier, when there is still a possibility to reverse the condition. CAN causes in some postural hypotension. There can also be peripheral blood flow alteration and cases of sudden death.

POSTURAL HYPOTENSION

A decrease in systolic BP more than 20 mm of Hg when patient gets up from sitting posture is the parameter for diagnosing postural hypotension. Treatment with TCA or diuretics therapy may exacerbate postural hypotension. Patients complaint of dizziness on standing but some patients have no symptoms. Postural hypotension is associated with increased mortality rate.[19]

TREATMENT

- Better glycaemic control by use of insulin or OHA's
- Slow change of posture and avoidance of sudden postural change.
- Use of Fludrocortisone in resistant cases in dose of 0.1 mg which can be gradually increased to maximal daily dose of 0.5 mg with renal function monitoring.
- Support stockings
- Midodrine
- Octreotide

ALTERATION IN PERIPHERAL BLOOD FLOW

Arterio- venous shunting in patients with autonomic neuropathy, causes prominence of veins in already neuropathic leg. Due to sympathetic denervation the venous oxygen tension, skin blood flow, and capillary pressure are increased. If there is no peripheral vascular disease it will be a warm foot. It is an important factor that causes osteopenia which leads to development of Charcot neuro-arthropathy.

CAN FUNCTION TESTS

	Normal	Borderline	Abnormal
Simple reflex tests			
Heart rate responses			
• to Valsalva manœuvre (15 secs)[1]: ratio of longest to shortest R–R interval	≥1.21		≤1.20
• to deep breathing (6 breaths over 1 min): maximum–minimum heart rate	≥15	11–14	≤10
• to standing after lying: ratio of R–R interval of 30th to 15th beats	≥1.04	1.01–1.03	≤1.00
Blood pressure response[2]			
• to standing: systolic BP fall (mmHg)	≤10	11–29	≥30
Specialised tests			
• Heart rate and blood pressure responses to sustained handgrip			
• Heart rate variability using power spectral analysis of ECG monitoring			
• Heart rate and blood pressure variability using time-domain analysis of ambulatory monitoring			
• MIBG (met-iodobenzylguanidine) scan of the heart			

AUTONOMIC GASTROPARESIS

Vagal denervation usually of stomach may be the cause. Autonomic neuropathy causes decrease in oesophageal motility leading to dysphagia, heart burn and gastroparesis. The reduction in gastric emptying causes bloating, early satiety, vomiting and swings between hypoglycaemia and hyperglycaemia.

Diagnosis is essentially clinical. Sometimes there is succusion splash. Investigations like barium swallow or gastroscopy can be helpful sometimes. Patients present with recurrent vomiting which causes dehydration, weight loss and frequent fluctuation in blood glucose.

TREATMENT

- Control of blood glucose fluctuations
- Metoclopramide and domperidone
- Drugs for gastric motility → Erythromycin
- Gastrostomy tube feeding
- Total parentral nutition

AUTONOMIC DIARRHOEA

It is an uncommon presentation and is rarely severe. This complication is caused by autonomic denervation which leads to abnormal gut motility, causing bacterial overgrowth and malabsorption.ther is troublesome diarrhoea which is more at night and there are stages of remissions and recurrences.

Faecal incontinence may set in. Constipation can also at times alternate with episodes of diarrhoea. Treatment is essentially conventional.

ABNORMAL SWEATING

It is the commonest symptom of DAN, it usually affect the face precipitated by food intake (Gustatory sweating).Glycopyrrolate can be used for topical application to treat gustatory sweating.

Reduced sweating in feet causes dry feet leading to fissuring and sometimes infection. Nocturnal sweating not related to hypoglycaemia can be another presentation.

NEUROPATHIC BLADDER

It is attributable to sacral nerve pathology. Usually patients are asymptomatic but may present with symptoms like hesistency and increased urinary frequency. Urinary retention or overflow incontinence can also be seen.

These patients are prone to urinary tract infections. Ultrasound screening, cystometrography, and intravenous urography are required for diagnosis. Treatment manoeuvres include frequent bladder emptying either by supra-pubic pressure or they can be taught intermittent self-catheterization. Treatment is by neostigmine, pyridostigmine.

ERECTILE DYSFUNCTION

Autonomic neuropathy contributes to diabetic erectile dysfunction, as does vascular disease. If no contraindication sildenafil can be used, or vacuum pumps or vaso-active drugs such as papaverine (with or without phentolamine) or drosvaglandin E can be used. Surgery is required, when large vessel is a significant contributor.

INVESTIGATION OF NEUROPATHY

CLINICAL MEASURES

- Assessment of signs and symptoms
- Careful neurologic examination
- In asymptomatic patients - horizontal graphic rating scale or a modification of the mcgill pain questionnaire

QUANTITATIVE SENSORY TESTING

- Vibration perception using hand-held biothesiometer
- Pressure sensation testing by Ten gram semmes-weinstein monofilament
- Tactile two-point discrimination
- Thermal testing

ELECTROPHYSIOLOGY

This is not only the most sensitive and reliable test for peripheral nerve function but also is a reproducible test which correlates well with nerve biopsy results. Abnormalities are not found specific to diabetes.

MORPHOLOGIC ASSESSMENT

Due to its invasive nature, difficulties in interpretation and problems with reproducibility, sural nerve biopsy for diagnosis of peripheral diabetic neuropathy is now obselete.

ACUTE AXONAL POLYNEUROPATHY

These syndromes are not common and are characterized by a sudden onset of pain affecting the feet and legs in a symmetrical manner. Two clinical syndromes have been identified

Painful polyneuropathy associated with poor glycaemic status and acute painful polyneuropathy associated with rapid improvement in glycaemic status though they are unrelated to other complications of chronic diabetes.

RAPIDLY REVERSIBLE HYPERGLYCEMIC NEUROPATHY

Rapidly reversible nerve conduction abnormalities can often be seen in recently diagnosed diabetics or chronic diabetics with transiently poorly controlled diabetes and often associated with transient symptoms. There are usually no structural abnormalities.

Improvement in glycaemic status leads to complete recovery. Ellenburg coined the term ‘neuropathic cachexia’, characterised by marked weight loss, severe pain typically of burning quality and persistent sometimes associated with contact pain (allodynia).

The rapid onset, the severity and the nocturnal exacerbation of symptoms often lead to depression. Motor signs are classically absent and ankle jerks are lost in few.

NCS usually normal or maybe abnormal sometimes. Temperature discrimination threshold often reduced in patients. Complete resolution occurs within a year, and weight gain is usual with improvement in glycaemic control using exogenous insulin.

RAPID GLYCAEMIC CONTROL RELATED ACUTE PAINFUL NEUROPATHY {‘INSULIN NEURITIS’}

This occurs with rapid improvement in glycaemic status either with use of insulin or OHA’s. It is characterised by burning pain, paraesthesia and allodynia, often with nocturnal exacerbation and depression. There is no associated weight loss. Loss of sensation may be mild or absent. There are no motor signs. NCS are normal but there is reduced exercise-induced increment of conduction velocity.

Symptoms completely resolve within a year. Under anaerobic conditions the hypoxic nerves use glucose. Once the glucose in blood is normalized, glucose is no longer available for nutrition, consequently, the nerves undergo axonal degeneration. Normalization of blood glucose slowly with insulin improves the symptoms.

PROXIMAL MOTOR NEUROPATHY (AMYOTROPHY)

Diabetic proximal motor neuropathy can be symmetric or asymmetric. Lower limbs are more frequently involved. The term "diabetic amyotrophy" is commonly used for this form of neuropathy. The presentation is unique.

In 1961, Garland coined the term "diabetic amyotrophy"[7]. The term diabetic proximal motor symmetric or asymmetric neuropathy has been proposed recently for this entity. *I*ncidence of diabetic amyotrophy (DA) is around 1.1% in T2DM and 0.3% in T1DM. Males in fifth and sixth decade are predominantly affected.

Proximal leg muscles are involved first, with symptoms like thigh pain, which is deep, achy, and at times jabbing. The pain is worse at night. The unilateral form is painful, and the bilateral form is less painful. Sensory symptoms such as paresthesias are unusual. Muscle weakness follows pain and weakness is first seen in quadriceps, glutei, iliopsoas,

hamstrings, and adductors. Weakness may remain unilateral or bilateral and muscle atrophy may develop later.

There are no fasciculations. Symmetric onset of DA is associated with generalized distal sensory motor polyneuropathy, less pain, slower progression, less weight loss, and frequently occurs in T1DM. Bowel and bladder function are spared. Knee jerks are absent.

Electrophysiologic findings show slowing of motor and sensory nerves distally. Prolongation of femoral nerve motor latency and decreasing amplitude of compound muscle action potential may be present. Needle EMG shows a neurogenic pattern in the affected muscles. Muscle biopsy shows neurogenic features.

Patients with DA improve within 6 to 12 months after controlling hyperglycemia but recovery is often incomplete. Pain resolves first and relapse occurs in 20% of cases. Root micro-infarction, degeneration of anterior horn cells, motor roots, or lumbosacral plexus are the common etiopathogenesis. Nerve biopsy studies show vasculitic infiltrate.

MONONEUROPATHIES

Isolated peripheral nerve lesions are present in diabetic patients, particularly in older individuals with T2DM. Mononeuropathies are acute in onset and associated with pain in peripheral nerves like peroneal, median, or ulnar, and occurs at sites of entrapment or external compression .

Cranial nerves particularly III and VI are most commonly affected. The exclusion of intracranial pathology, particularly malignancy or aneurysms, before making diagnosis of a diabetic cranial mononeuropathy is a must.

Mononeuropathies gradually improve without any specific treatment, but surgical decompression may be required in certain entrapment neuropathies.

DIABETIC MONONEUROPATHY MULTIPLEX

Mononeuropathy multiplex has an abrupt onset, with pain, paresthesias, and motor weakness. Motor axons are predominantly affected. The diagnosis is based on two or more nerves involved at different time intervals and locations. Electrophysiologic studies are consistent with axonal neuropathy.

DIABETIC CRANIAL NEUROPATHY

The third cranial nerve palsy is the most common diabetic mononeuropathy. Patients present with orbital pain, drooping of eyelid or frontal headache. On examination, partial ptosis and ophthalmoplegia is seen with pupillary sparing . Complete recovery usually occurs within three months, which sugests vascular aetiology.

Pupillary response is spared because parasympathetic nerve fibers, which run at the periphery of the third nerve, are not affected because the ischemia affects the central portion of the nerve.

Exclusion of other causes of third cranial nerve palsy like aneurysm or tumour with the help of computerized tomographic or magnetic resonance imaging is important. Paralysis of sixth and seventh cranial nerve, are comparatively less common in diabetics.

TRUNCAL NEUROPATHY

Predominatly affects the elderly. Diabetic truncal radiculopathies present with sudden pain which is suggestive of vascular cause. Distribution of pain is in the region of lower thorax or abdomen. The pain is mostly asymmetrical.

Exclusion of other condition which may lead to nerve root compression is important. Diagnosis can be difficult in those with abdominal pain and some patients may undergone unnecessary investigations like barium enema or colonoscopy. patients may land up with laparotomy. Careful history taking and through clinical examination is key to diagnosis.

Patient can be reassured strongly as complete recovery is usual within a year, although occasionally symptoms can be persistent for years.Diabetic thoracolumbar or thoracoabdominal neuropathy / radiculopathy affects older diabetics (>50 years).

It is more common in T2DM and most patients give a history of significant weight loss. The syndrome was first described by Longstreth and colleagues in four diabetic patients who were evaluated extensively for abdominal pain. The onset of symptoms is chest and/or abdominal pain, more intense at night. Pain may radiate to the thigh or back and rarely to the neck.

The skin over the chest or abdominal wall becomes sensitive to the touch. Unless the diagnosis is made early, most patients are subjected to extensive, expensive, and at times invasive procedures to rule out an

underlying carcinoma because of their age and unexplained pain with weight loss.

The pain is intermittent and usually unilateral, although it may progress bilaterally. The pain is usually in the region of thoracolumbar roots. Sensory deficits usually have a dermatomal distribution. Involvement of the lumbar root may present with abdominal wall muscle weakness and herniation.

Thoracolumbar neuropathy can present at the initial onset of diabetes. The diagnosis is based on a history of diabetes, weight loss, and the clinical features.

Electrophysiologic studies often reveal evidence of generalized polyneuropathy. Needle EMG of the thoracic, lumbar, or abdominal wall muscles may show denervation changes.

Controlling the glycemic state and improvement of the nutritional condition of the patient are the mainstays of treatment. Antidepressant or antiepileptic drugs may be used for pain control. Remission may occur within 6 to 12 months.

ENTRAPMENT NEUROPATHIES

Pressure (entrapment) neuropathies affecting the median and ulnar nerve are more common in the diabetic population than in the general population. Median nerve entrapment (carpal tunnel syndrome) cause pain and even paraesthesiae in hands. This can radiate to forearm, and is more marked at night.

Examination reveals a reduction of sensation in the median territory of the hand (lateral 3½ fingers) and muscle wasting in the region of thenar eminence. Diagnosis of carpel tunnel syndrome can be confirmed by median NCS.

Surgical decompression is the treatment of choice. Patients usually respond well to surgical decompression but occasionally painful symptoms may relapse.Ulnar nerve entrapment at the ulnar groove in the elbow can also cause wasting of dorsal interossia, especially first.

Ulnar electrophysiological studies can isolate the site of lesion and help confirm the diagnosis. Other nerves that are vulnerable to entrapment are the lateral popliteal nerve which results in foot drop, the

radial nerve which can result in wrist drop and the lateral cutaneous nerve of the thigh causing meralgiaparaesthetica.

The occurance of carpal tunnel syndrome in diabetes is estimated to be 23.3%. Electrophysiologic evidence of carpal tunnel syndrome in asymptomatic patients is about 27%. Ulnar nerve entrapment at the elbow is more frequent. The diagnosis of entrapment neuropathy is confirmed by electrophysiologic testing.

TREATMENT

Management of Painful Diabetic Neuropathy

- Exclusion of other causes of neuropathy
- Psychological support for the patient
- Non pharmacological treatments: for example, bed cradle, opsite for contact pain
- Pharmacological treatments
    - Optimization of glycaemic control
    - Tricyclic antidepressants (imipramine or amitriptyline, 25-150 mg taken at night; SSRIs if tricyclics are not well tolerated)
    - Anticonvulsants (gabapentin 900-3600 mg/day in divided doses, carbamazepine 200-800 mg/day)

- Tramadol (50-400 mg/day)
- Capsaicin cream (0.075%)
- IV lignocaine (0.5 mg/kg given over 30 min)
- Aldose reductase inhibitors
- α lipoic acid

- Electric spinal cord stimulation if no response or if there are unacceptable side effects to pharmacotherapy
- Transcutaneous electric nerve stimulation (TENS)

CANS ANALYSER

CANS analyser is an important tool to measure and diagnose autonomic dysfunction using R-R intervals of ECG and automatic BP measurements. The test procedure are guided by computer software and both cardiac sympathetic and parasympathetic autonomic functions are analysed.

CLINICAL TESTING OF AUTONOMIC NEUROPATHY :

Quantitative tests to assess autonomic function show less advancement than those used to assess the functions and deficits of motor and sensory nerves.[10]

It was believed that autonomic neuropathy had little if any contribution and correlation to peripheral neuropathies which commonly affect diabetic patients. More than forty years back the following five simple and noninvasive tests to assess cardiovascular reflex were proposed.

Test (in following order)	Position	Approximate time of test (min)	Apparatus required
Heart-rate response to Valsalva manoeuvre	Sitting	5	Aneroid manometer, electrocardiograph
Heart-rate variation during deep breathing	Sitting	2	Electrocardiograph
Blood-pressure response to sustained handgrip	Sitting	5	Handgrip dynamometer, sphygmomanometer
Immediate heart-rate response to standing	Lying to standing	3	Electrocardiograph
Blood-pressure response to standing	Lying to standing	3	Sphygmomanometer

The above mentioned tests have been utilized successfully in a number of studies and for assessment of patients with features suggestive of autonomic dysfunction.

It is mandatory to rule out end organ damage before subjecting the patient to these tests. They are valid, specific and significant time tested procedures to diagnose autonomic neuropathy noninvasively.

Co-morbid illness, use of drugs like anti-histamines, anti-tussives, antidepressants, diuretics and aspirin should not be there. Patients are advised to abstain from smoking and drinking coffee at least one hour before the test.

Heart rate response to deep breathing

Heart rate varies with respiration and this is determined by the parasympathetic system. To assess this response, patient is instructed to lie down quietly and is told to take slow deep breaths at a rate of six per minute. ECG monitors maximum and minimum heart rate.

Heart rate response to standing

The patient is asked to get up from lying posture and heart rate to this response is assessed. After standing, the heart rate normally increases and is maximum at about fifteenth beat after attaining vertical posture. The heart rate then starts falling and is minimum at about thirtieth beat. Hence R-R variation between fifteen and thirtieth beats ate assessed.[23]

Valsalva maneuver

Originally used as a method to expel pus from middle ear which is done by blowing and straining with closed nose and mouth. The patient

first takes a deep breath and then expires forcibly against a closed glottis for a period of ten to twenty seconds.

Alternatively to test for autonomic function, patient needs to blow into a sphygmomanometer such that a pressure level of at least forty mms is maintained for thirty seconds. Valsalva maneuver is associated with a short duration increase of intraocular pressure as well as intra cranial pressure. This leads to a risk of hemorrhage within the eye and dislocation of lens. The risk is somehow known to be low because similar increase in pressure occur in day to day activities also.

There are four phases described as normal response to valsalva maneuver.

Phase 1: at the beginning of straining, there is a short duration of increase in intrathoracic pressure which causes increased BP and decreased heart rate. This happens because the elevated pressure compresses the aorta thereby propelling blood into peripheral circulation.

Phase 2: This is the straining phase where there is decrease in BP initially which later is recovered. There is associated reflex tachycardia, stroke volume reduces because of decrease in venous return.

Phase 3: cessation of straining in this phase causes an increase in venous return. There is an abrupt but transient fall in BP and increased heart rate.

Phase 4: this is the overshoot phase where the event returns to pre-valsalva state after about 6 to 8 beats. There is an initial overshoot of BP wide pulse pressure and also reflex bradycardia. ECG tracing during the maneuver are taken to calculate ratio between longest and shortest R-R interval. Normal is 1.6.

Systolic blood pressure response to standing

Otherwise known as postural hypotension and has been discussed earlier.

Diastolic BP response to sustained handgrip

A hand grip dynamometer is used to detect increase of systolic and diastolic BP and chang in heart rate. The patient is supposed to squeeze the dynamometer to its maximum followed by a slow release to keep it at a level of at least 30 % of maximum for 120 to 180 seconds. Normally after the hand grip is released, there will be an increase of diastolic BP to more than 16 mm of Hg. Abnormal response is less than 10 mm of Hg increase in BP.

We look for reduced variability (less of a change in heart rate), a sign that the patient's heart response, as provided by the body's autonomic control center, is not adequate. At least two tests must be performed in order for the test to be conclusive. Sometimes one test result may be abnormal, but the second test result turns out normal.

This is because some heart rate variability tests are more sensitive to earlier autonomic nervous system dysfunction than others. This is also due to the fact that test results are based on a combination of activities within the body, which are influenced differently in each patient. As a general rule, the more tests that result in abnormal results, the more severe the end organ damage is to the autonomic nervous system.

Perhaps the most important things we can do for our patients with diabetes are to make them aware of autonomic neuropathy, to let them know whether they have it, and to help them keep blood sugar levels in an acceptable range.

Doing so not only helps reduce the risk of heart disease, but also lowers the risk of diabetic eye, kidney and nerve disease, each of which patients want to avoid.

Diabetic autonomic neuropathy has been called a "silent killer," because so few patients realize that they suffer from it, and yet its effects can be so lethal. With a brief, 15-minute test that we can administer in the office, and some relatively modest interventions, we can help many patients live longer, healthier lives.

MATERIAL AND METHODS

SETTING

This study was conducted at the Institute of Diabetology, Rajiv Gandhi Government General Hospital and Madras Medical College.

ETHICAL COMMITTEE APPROVAL

Obtained.

STUDY DURATION

This study was conducted over a period of four months.

STUDY POPULATION

Patients attending Diabetology outpatient department at Institute of Diabetology.

SAMPLE SIZE

Hundred and two T2DM patients who attended outpatient department.

TYPE OF STUDY

Observational study.

INCLUSION CRITERION

- Patients diagnosed with Type 2 Diabetes Mellitus of any duration.
- Patients equal to or more than 30 years of age and less than 70 years

EXCLUSION CRITERIA

- Type 1 Diabetes Mellitus
- Gestational Diabetes Mellitus
- Secondary Diabetes Mellitus
- Patients on pacemakers
- Patients on anti-arrythmic drugs
- Patients with self reported neurological disease.
- Patients with known cardiac disease
- Patients less than 30 years and more than 70 years

ANALYSIS PLAN

- Chi square test
- SPSS version 17.0

DATA COLLECTION AND METHODS

Informed consent was obtained from each patient or the relative.

Patients had their history taken according to a Questionnaire and were subjected to clinical examination.

Patients were subjected to investigations like

Renal function tests

Plasma glucose

HbA1c

Urine microalbuminuria

Cardiac autonomic neuropathy testing

Biothesiometry

Fundus examination of the eye

All data was entered in proforma and master chart prepared for data analysis.

Data was analysed using XlStat

Renal function tests: Serum creatinine was done by Jaffe's method

Plasma glucose was done by glucose oxidation method

HbA1c by High pressure liquid chromatography

Urine PCR: urine proteins determined by turbidimetric method using 3% sulphosalicylic acid and creatinine by Jaffe's method.

All the investigation were done at lab of Institute of Diabetology by well trained technicians

Cardiac autonomic neuropathy testing using CANS analyser with software.

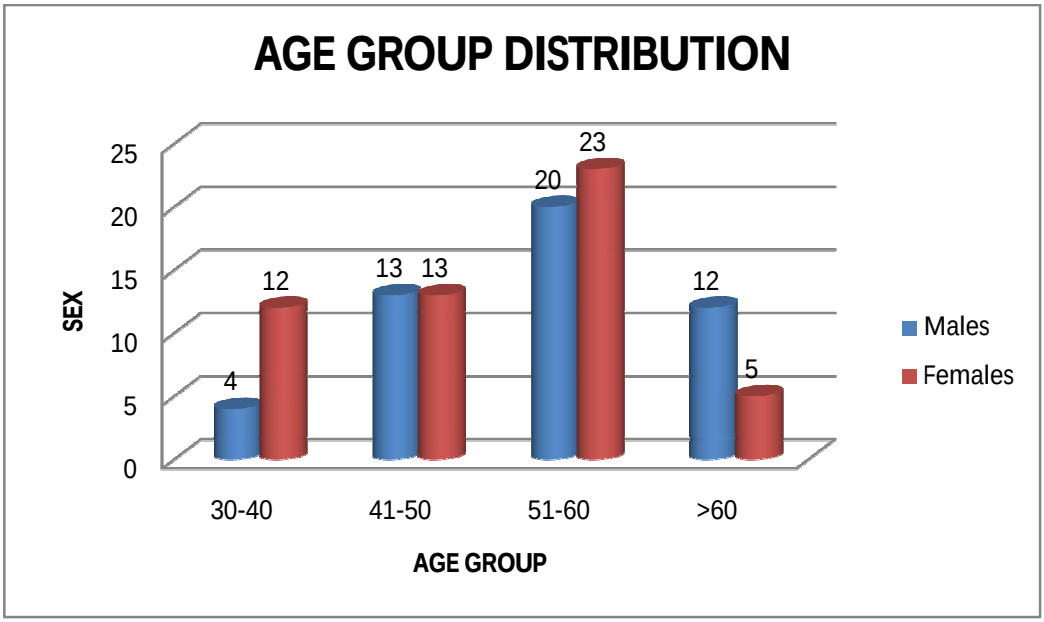
Biothesiometry by Biothesiometer with software

Fundus examination of the eye by ophthalmologist at Regional Institute of Ophthalmology, Egmore.

OBSERVATION AND RESULTS

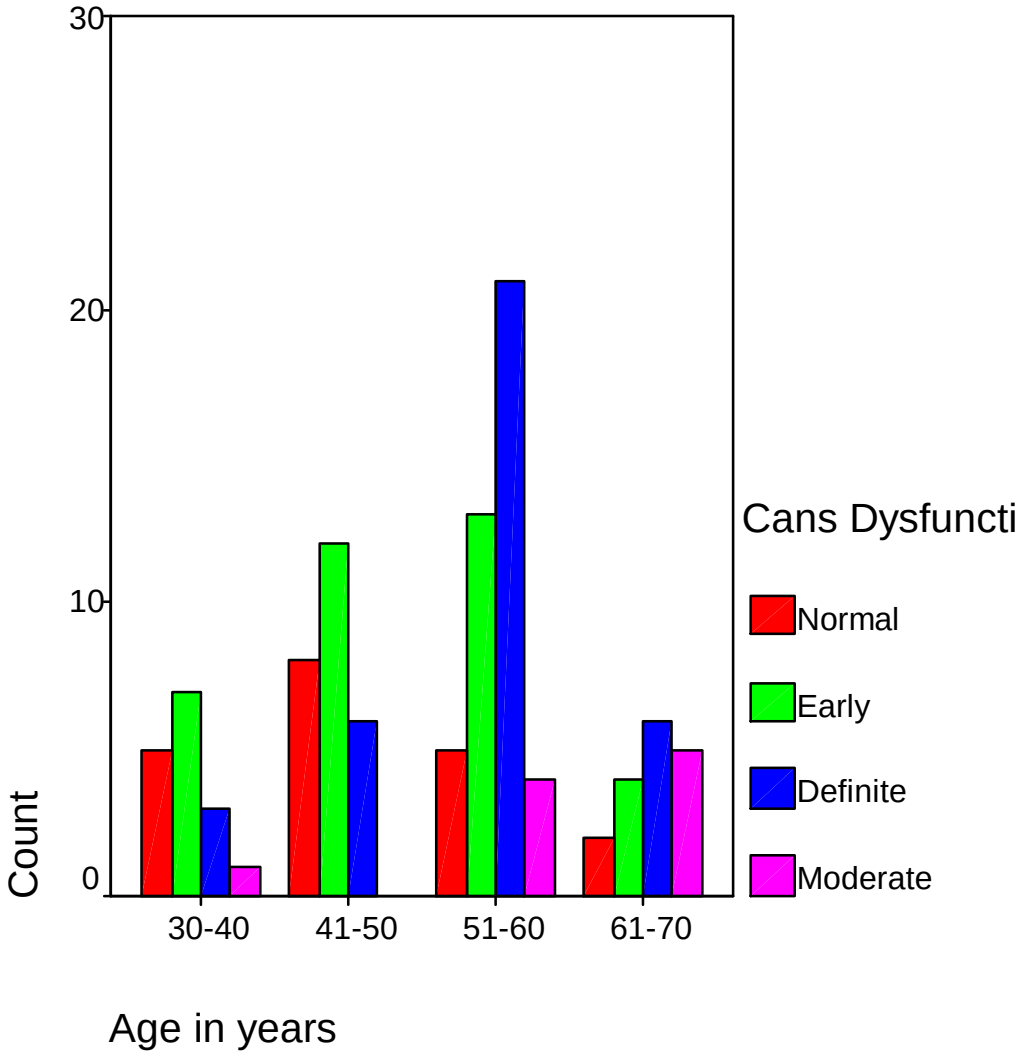
AGE DISTRIBUTION

AGE GROUP(years)	MALES	FEMALES
30-40	4	12
41-50	13	13
51-60	20	23
61 – 70	12	5



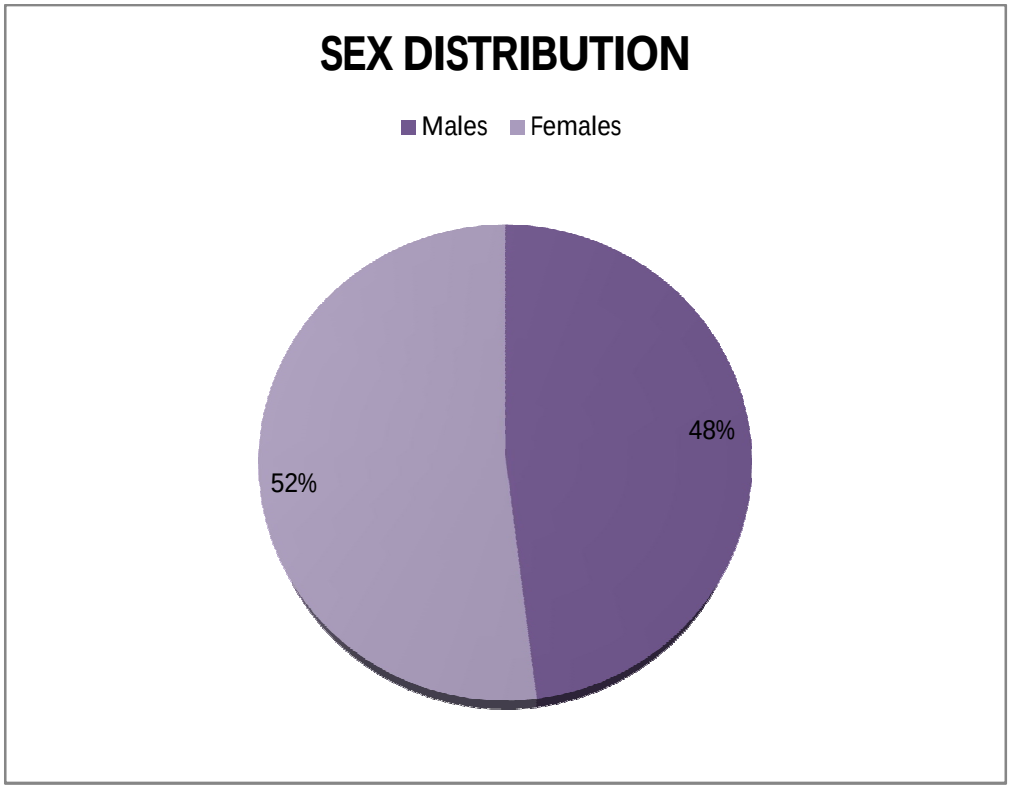
AGE AND CANS

			Cans Dysfunction				Total	P value
			Normal	Early	Definite	Moderate		
Age in years	30-40	Count	5	7	3	1	16	
		% within Age in years	31.3%	43.8%	18.8%	6.3%	100.0%	
		% within Cans Dysfunction	25.0%	19.4%	8.3%	10.0%	15.7%	
	41-50	Count	8	12	6	0	26	
		% within Age in years	30.8%	46.2%	23.1%	.0%	100.0%	
		% within Cans Dysfunction	40.0%	33.3%	16.7%	.0%	25.5%	0.013*
	51-60	Count	5	13	21	4	43	
		% within Age in years	11.6%	30.2%	48.8%	9.3%	100.0%	
		% within Cans Dysfunction	25.0%	36.1%	58.3%	40.0%	42.2%	
	61-70	Count	2	4	6	5	17	
		% within Age in years	11.8%	23.5%	35.3%	29.4%	100.0%	
		% within Cans Dysfunction	10.0%	11.1%	16.7%	50.0%	16.7%	
Total		Count	20	36	36	10	102	
		% within Age in years	19.6%	35.3%	35.3%	9.8%	100.0%	
		% within Cans Dysfunction	100.0%	100.0%	100.0%	100.0%	100.0%	


30
20
10
0
Count
30-40
41-50
51-60
61-70
Age in years
Cans Dysfuncti
Normal
Early
Definite
Moderate

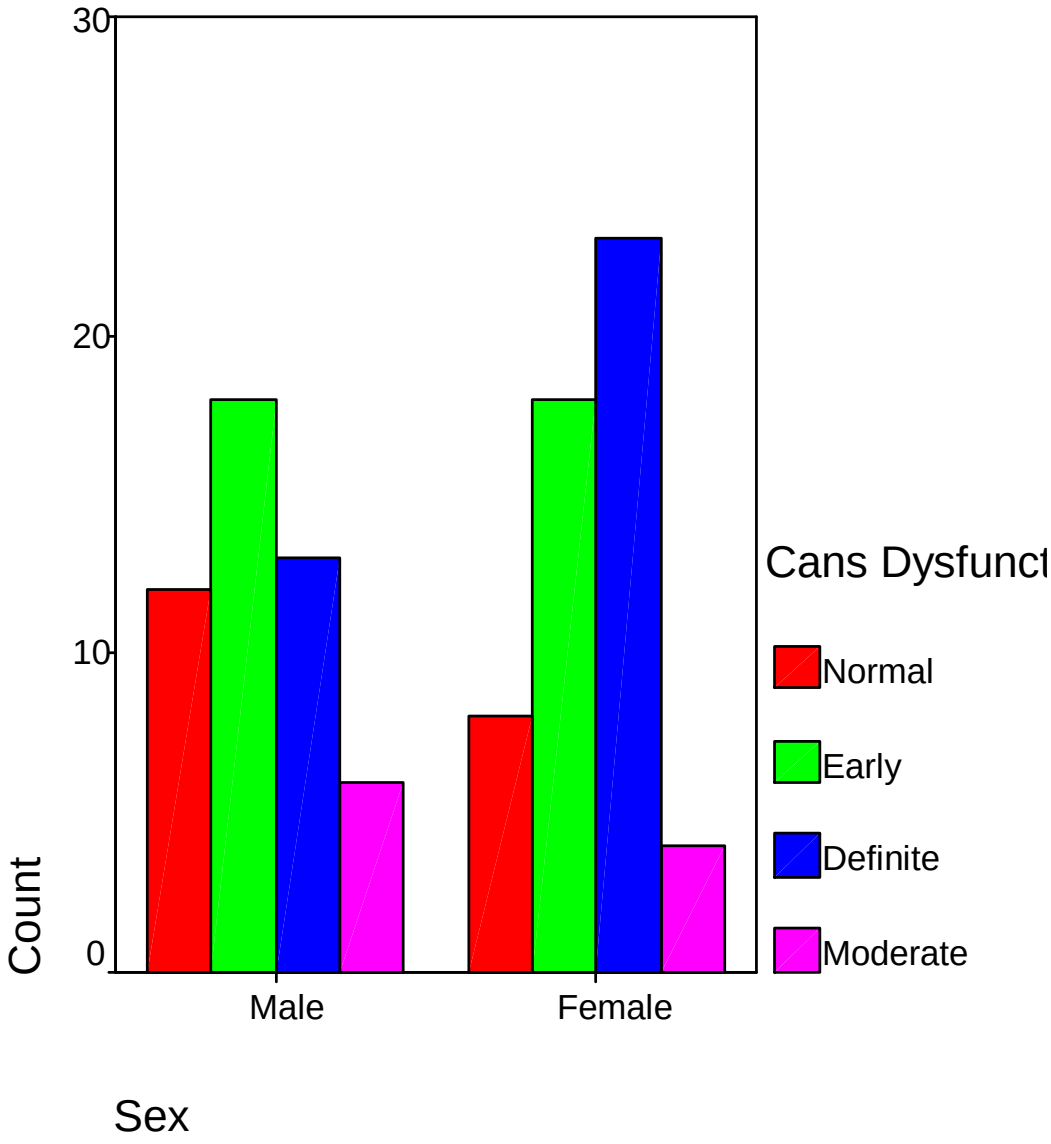
SEX DISTRIBUTION

SEX	NO. OF CASES	PERCENTAGES
MALE	49	48
FEMALE	53	52



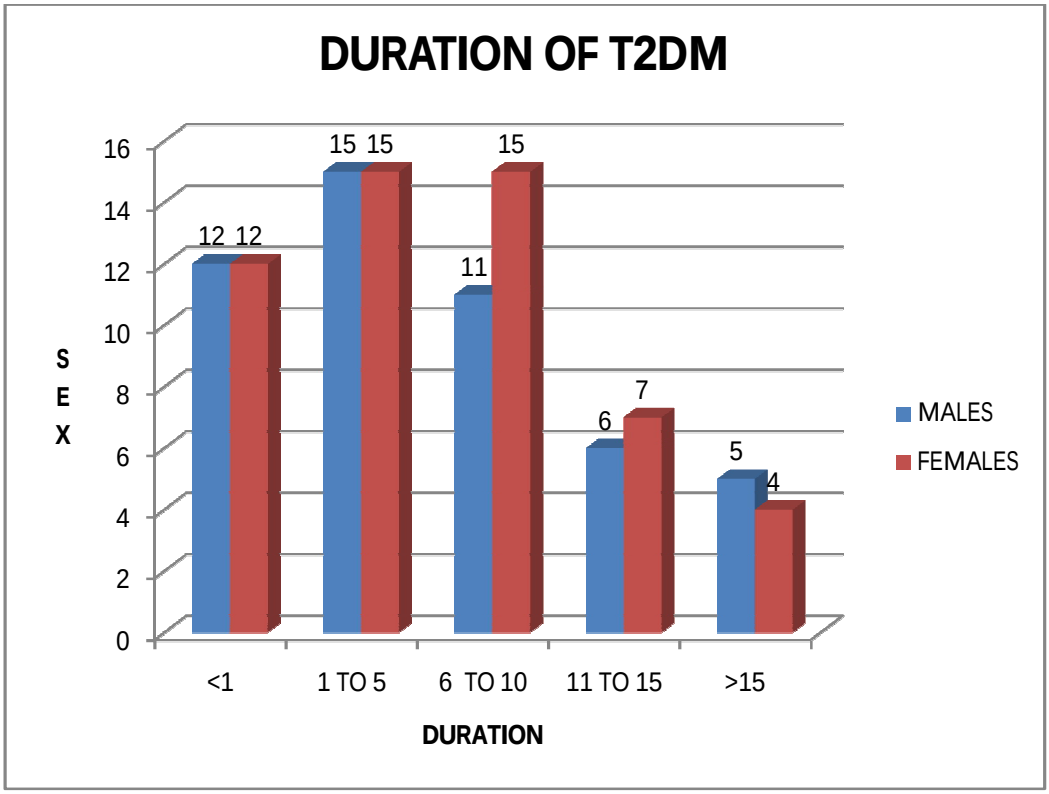
SEX DISTRIBUTION AND CANS

			Cans Dysfunction				Total	P value
			Normal	Early	Definite	Moderate		
Sex	Male	Count	12	18	13	6	49	
		% within Sex	24.5%	36.7%	26.5%	12.2%	100.0%	
		% within Cans Dysfunction	60.0%	50.0%	36.1%	60.0%	48.0%	
	Female	Count	8	18	23	4	53	
		% within Sex	15.1%	34.0%	43.4%	7.5%	100.0%	0.173
		% within Cans Dysfunction	40.0%	50.0%	63.9%	40.0%	52.0%	
Total		Count	20	36	36	10	102	
		% within Sex	19.6%	35.3%	35.3%	9.8%	100.0%	
		% within Cans Dysfunction	100.0%	100.0%	100.0%	100.0%	100.0%	


30
20
10
0
Count
Male
Female
Sex
Cans Dysfunct
Normal
Early
Definite
Moderate

DURATION OF T2DM (IN YEARS)

	<1	1 TO 5	6 TO 10	11 TO 15	>15
MALES	12	15	11	6	5
FEMALES	12	15	15	7	4

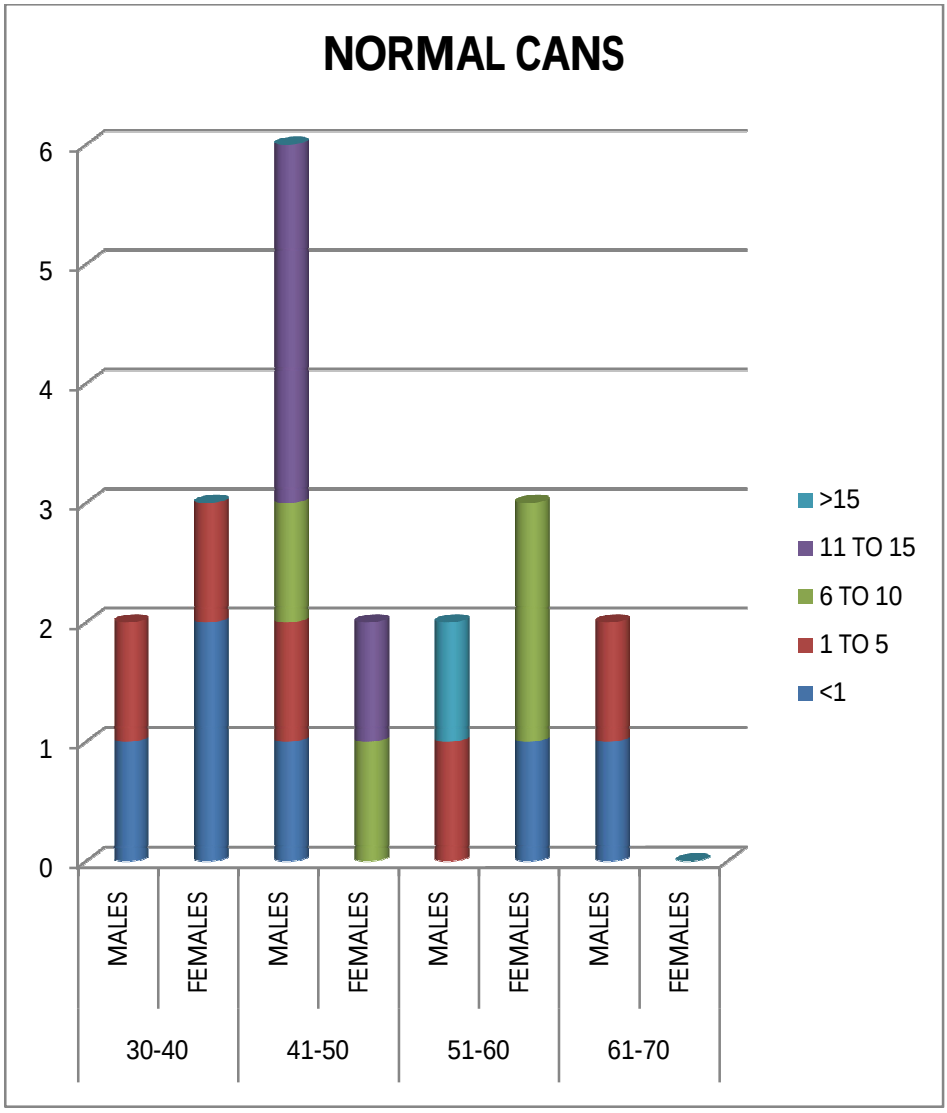


DURATION OF T2DM AND CANS

			Cans Dysfunction				Total	P value
			Normal	Early	Definite	Moderate		
Duration in years	< 1	Count	5	10	7	1	23	
		% within Duration in years	21.7%	43.5%	30.4%	4.3%	100.0%	
		% within Cans Dysfunction	25.0%	27.8%	19.4%	10.0%	22.5%	
	1-5	Count	6	11	12	2	31	
		% within Duration in years	19.4%	35.5%	38.7%	6.5%	100.0%	
		% within Cans Dysfunction	30.0%	30.6%	33.3%	20.0%	30.4%	
	6-10	Count	4	10	9	3	26	
		% within Duration in years	15.4%	38.5%	34.6%	11.5%	100.0%	
		% within Cans Dysfunction	20.0%	27.8%	25.0%	30.0%	25.5%	0.772
	11-15	Count	4	3	3	3	13	
		% within Duration in years	30.8%	23.1%	23.1%	23.1%	100.0%	
		% within Cans Dysfunction	20.0%	8.3%	8.3%	30.0%	12.7%	
	> 15	Count	1	2	5	1	9	
		% within Duration in years	11.1%	22.2%	55.6%	11.1%	100.0%	
		% within Cans Dysfunction	5.0%	5.6%	13.9%	10.0%	8.8%	
Total		Count	20	36	36	10	102	
		% within Duration in years	19.6%	35.3%	35.3%	9.8%	100.0%	
		% within Cans Dysfunction	100.0%	100.0%	100.0%	100.0%	100.0%	

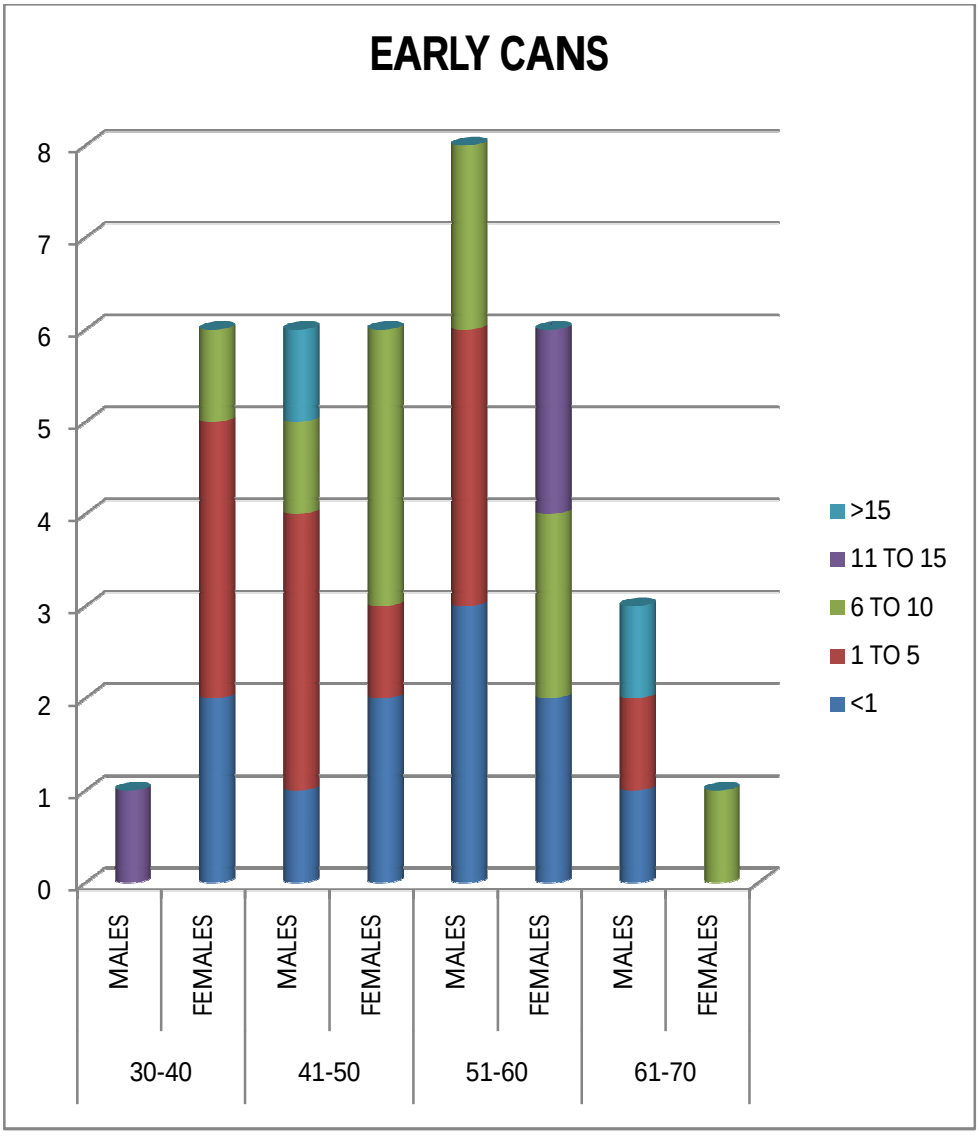
NORMAL CANS

	30-40		41-50		51-60		61-70	
	Males	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
<1	1	2	1	0	0	1	1	0
1 TO 5	1	1	1	0	1	0	1	0
6 TO 10	0	0	1	1	0	2	0	0
11 TO 15	0	0	3	1	0	0	0	0
>15	0	0	0	0	1	0	0	0


NORMAL CANS
6
5
4
3
2
1
0
MALES
FEMALES
MALES
FEMALES
MALES
FEMALES
MALES
FEMALES
30-40
41-50
51-60
61-70
>15
11 TO 15
6 TO 10
1 TO 5
<1

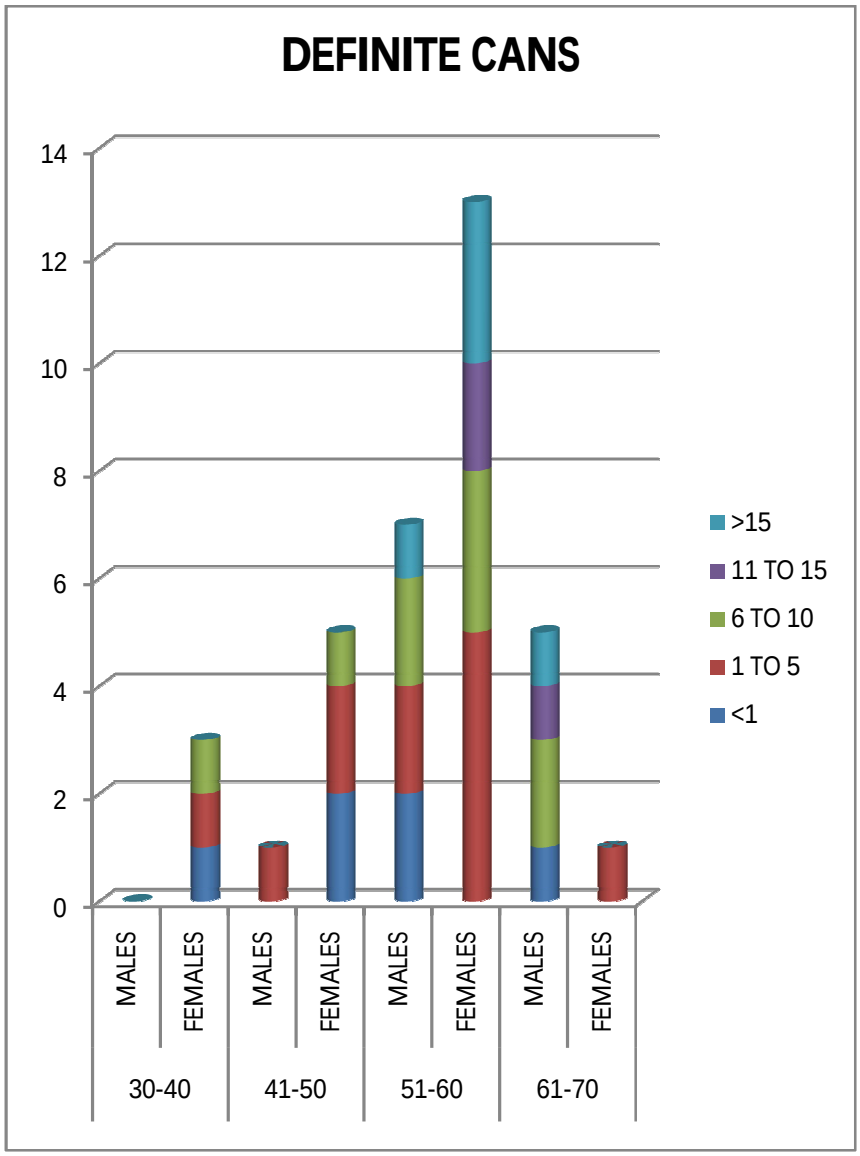
EARLY CANS

	30-40		41-50		51-60		61-70	
	Males	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
<1	0	2	1	2	3	2	1	0
1 TO 5	0	3	3	1	3	0	1	0
6 TO 10	0	1	1	3	2	2	0	1
11 TO 15	1	0	0	0	0	2	0	0
>15	0	0	1	0	0	0	1	0


EARLY CANS
8
7
6
5
4
3
2
1
0
MALES
FEMALES
MALES
FEMALES
MALES
FEMALES
MALES
FEMALES
30-40
41-50
51-60
61-70
>15
11 TO 15
6 TO 10
1 TO 5
<1

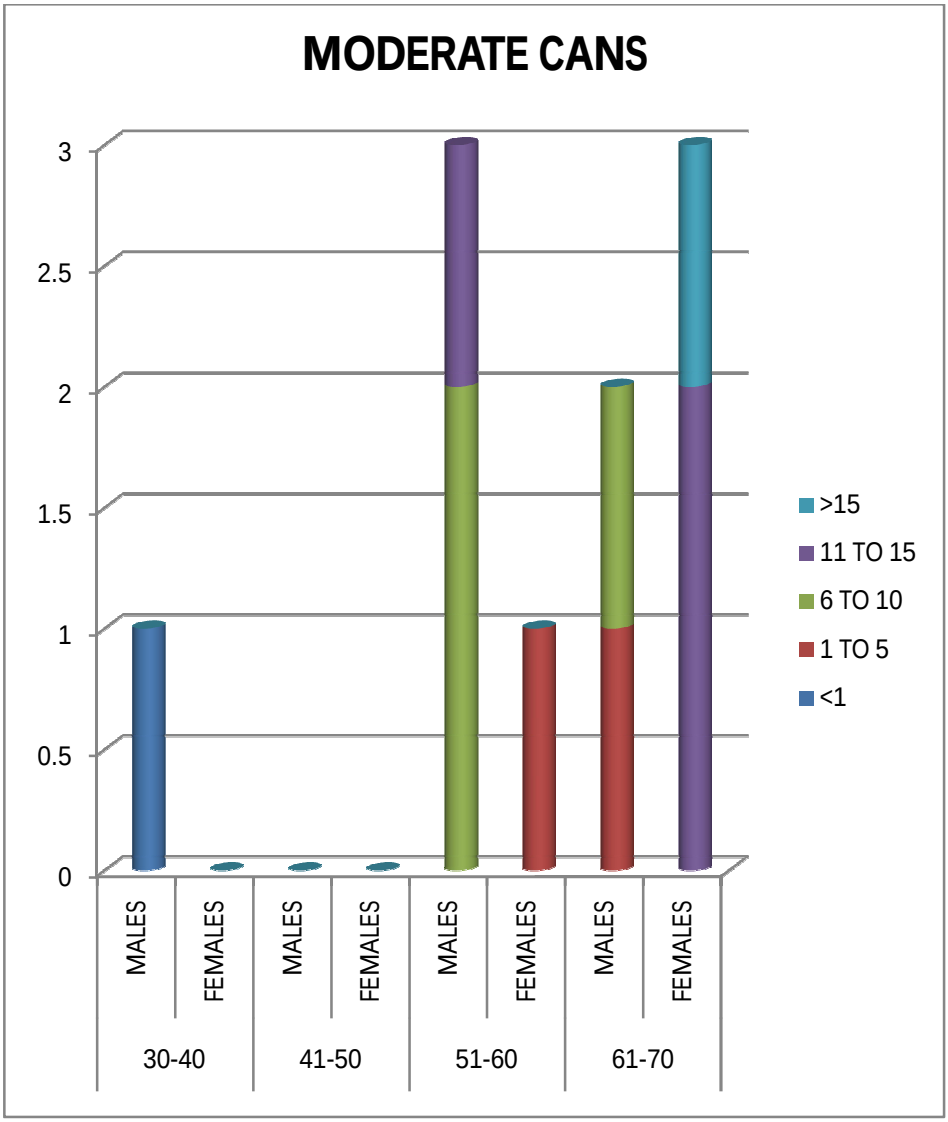
DEFINITE CANS

	30-40		41-50		51-60		61-70	
	Males	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
<1	0	1	0	2	2	0	1	0
1 TO 5	0	1	1	2	2	5	0	1
6 TO 10	0	1	0	1	2	3	2	0
11 TO 15	0	0	0	0	0	2	1	0
>15	0	0	0	0	1	3	1	0


DEFINITE CANS
14
12
10
8
6
4
2
0
MALES
FEMALES
MALES
FEMALES
MALES
FEMALES
MALES
FEMALES
30-40
41-50
51-60
61-70
>15
11 TO 15
6 TO 10
1 TO 5
<1

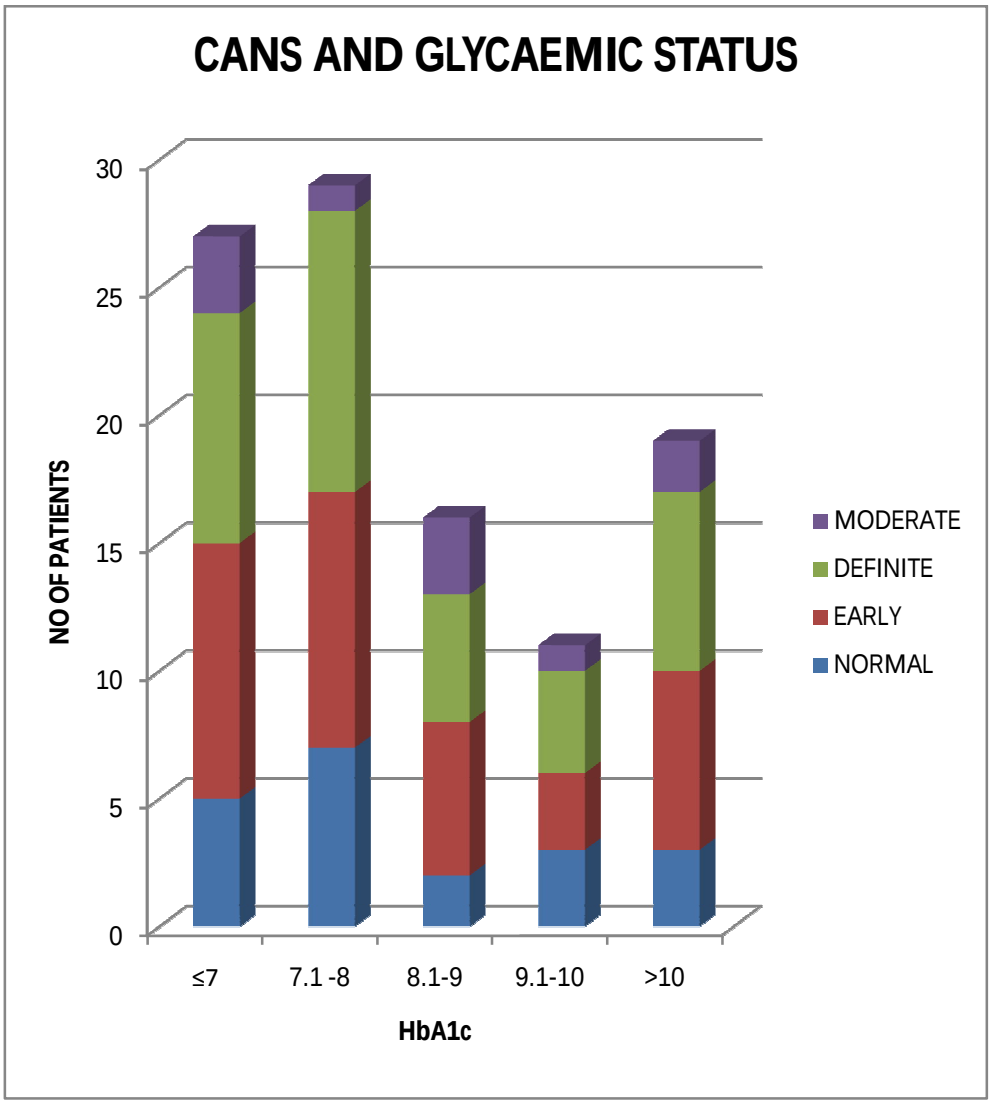
MODERATE CANS

	30-40		41-50		51-60		61-70	
	Males	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
<1	1	0	0	0	0	0	0	0
1 TO 5	0	0	0	0	0	1	1	0
6 TO 10	0	0	0	0	2	0	1	0
11 TO 15	0	0	0	0	1	0	0	2
>15	0	0	0	0	0	0	0	1


MODERATE CANS
3
2.5
2
1.5
1
0.5
0
MALES
FEMALES
MALES
FEMALES
MALES
FEMALES
MALES
FEMALES
30-40
41-50
51-60
61-70
>15
11 TO 15
6 TO 10
1 TO 5
<1

CANS AND GLYCAEMIC STATUS

HbA1c	NORMAL	EARLY	DEFINITE	MODERATE
≤7	5	10	9	3
7.1 -8	7	10	11	1
8.1-9	2	6	5	3
9.1-10	3	3	4	1
>10	3	7	7	2

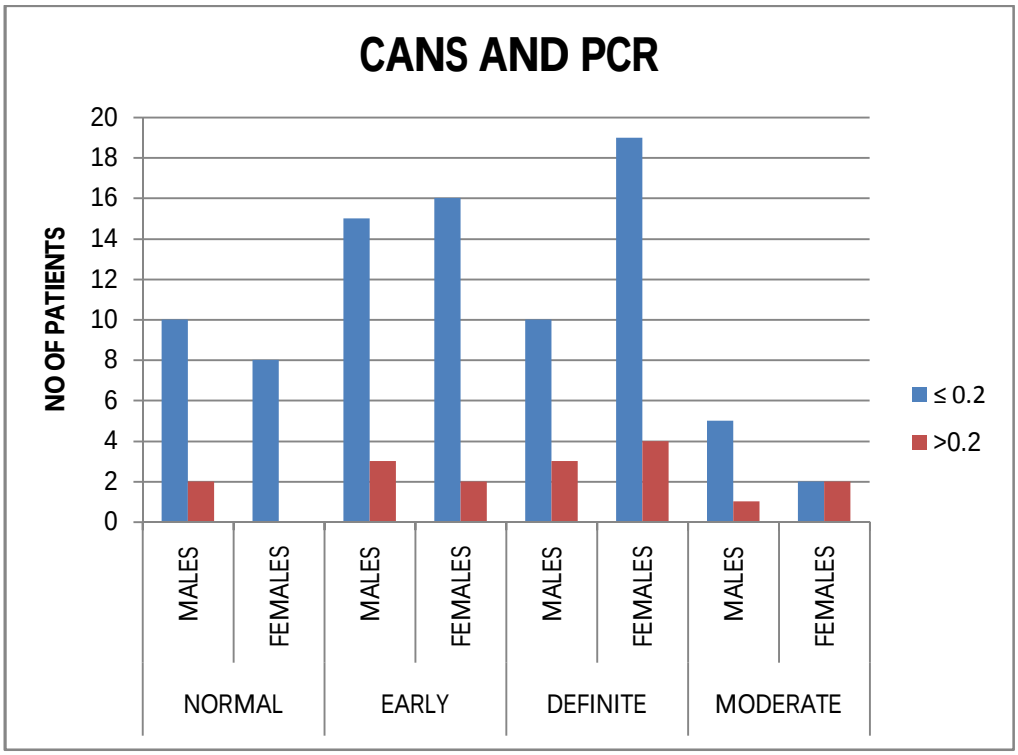

CANS AND GLYCAEMIC STATUS
NO OF PATIENTS
30
25
20
15
10
5
0
≤7
7.1 -8
8.1-9
9.1-10
>10
HbA1c
MODERATE
DEFINITE
EARLY
NORMAL

HbA1c AND CANS

			Cans Dysfunction				Total	P value
			Normal	Early	Definite	Moderate		
HBA1c	<= 7	Count	5	10	9	3	27	
		% within HBA1c	18.5%	37.0%	33.3%	11.1%	100.0%	
		% within Cans Dysfunction	25.0%	27.8%	25.0%	30.0%	26.5%	
	7.1-8	Count	7	10	11	1	29	
		% within HBA1c	24.1%	34.5%	37.9%	3.4%	100.0%	
		% within Cans Dysfunction	35.0%	27.8%	30.6%	10.0%	28.4%	
	8.1-9	Count	2	6	5	3	16	
		% within HBA1c	12.5%	37.5%	31.3%	18.8%	100.0%	
		% within Cans Dysfunction	10.0%	16.7%	13.9%	30.0%	15.7%	0.827
	9.1-10	Count	3	3	4	1	11	
		% within HBA1c	27.3%	27.3%	36.4%	9.1%	100.0%	
		% within Cans Dysfunction	15.0%	8.3%	11.1%	10.0%	10.8%	
	> 10	Count	3	7	7	2	19	
		% within HBA1c	15.8%	36.8%	36.8%	10.5%	100.0%	
		% within Cans Dysfunction	15.0%	19.4%	19.4%	20.0%	18.6%	
Total		Count	20	36	36	10	102	
		% within HBA1c	19.6%	35.3%	35.3%	9.8%	100.0%	
		% within Cans Dysfunction	100.0%	100.0%	100.0%	100.0%	100.0%	

CANS AND NEPHROPATHY (PCR)

PCR	NORMAL		EARLY		DEFINITE		MODERATE	
	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES
≤ 0.2	10	8	15	16	10	19	5	2
>0.2	2	0	3	2	3	4	1	2

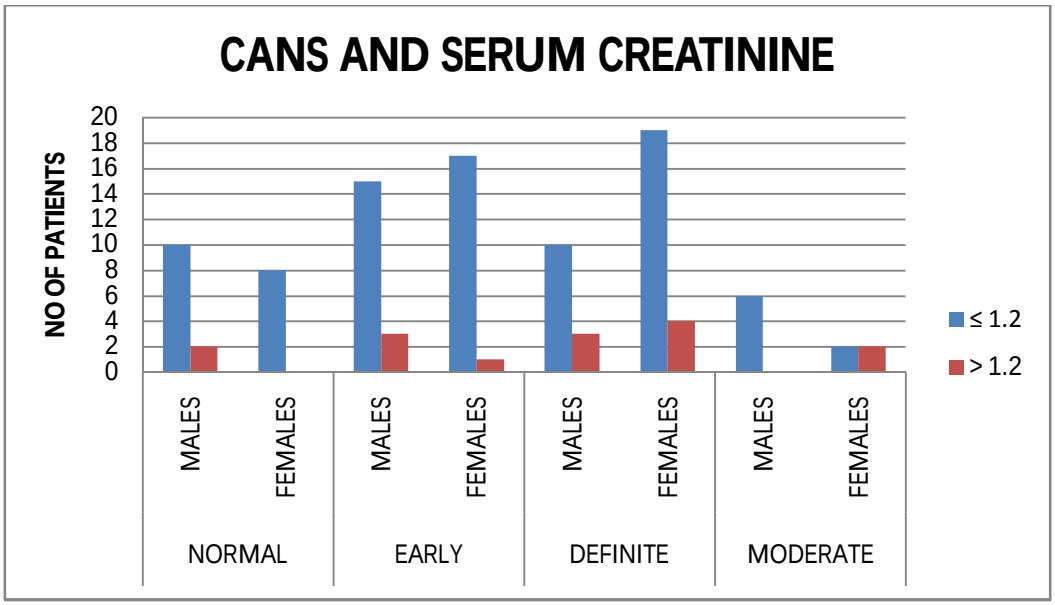


PCR AND CANS

			Cans Dysfunction				Total	
			Normal	Early	Definite	Moderate		
UPCR	Normal	Count	18	31	29	7	85	
		% within UPCR	21.2%	36.5%	34.1%	8.2%	100.0%	
		% within Cans Dysfunction	90.0%	86.1%	80.6%	70.0%	83.3%	
	Abnormal	Count	2	5	7	3	17	0.301
		% within UPCR	11.8%	29.4%	41.2%	17.6%	100.0%	
		% within Cans Dysfunction	10.0%	13.9%	19.4%	30.0%	16.7%	
Total		Count	20	36	36	10	102	
		% within UPCR	19.6%	35.3%	35.3%	9.8%	100.0%	
		% within Cans Dysfunction	100.0%	100.0%	100.0%	100.0%	100.0%	

CANS AND NEPHROPATHY (SERUM CREATININE)

SERUM	**NORMAL**		**EARLY**		**DEFINITE**		**MODERATE**	
CR	MALES	**FEMALES**	**MALES**	**FEMALES**	**MALES**	**FEMALES**	**MALES**	**FEMALES**
≤ 1.2	10	8	15	17	10	19	6	2
> 1.2	2	0	3	1	3	4	0	2

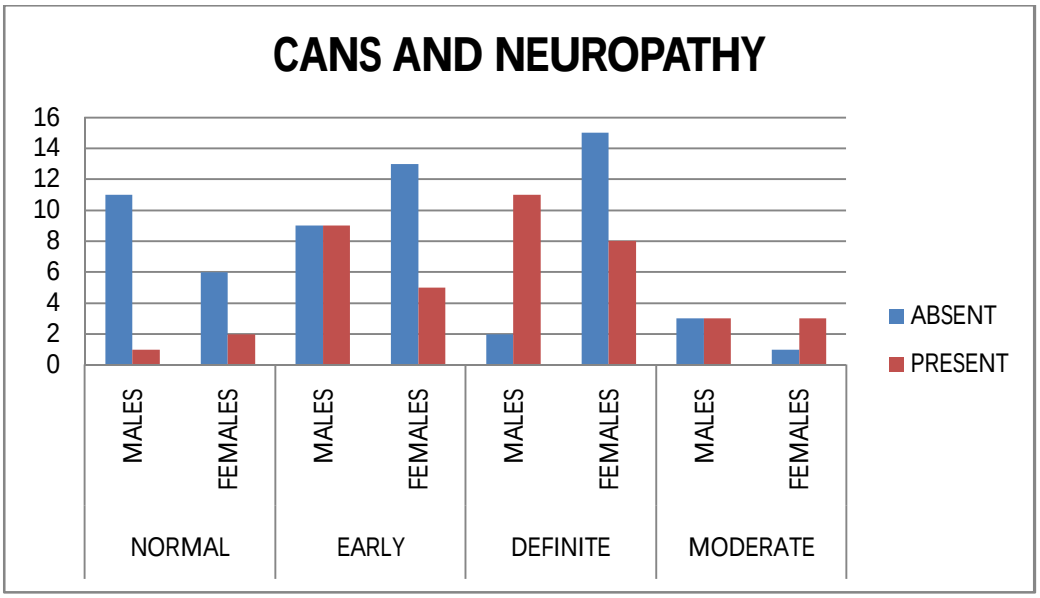


SERUM CREATININE AND CANS

			Cans Dysfunction				Total	P value
			Normal	Early	Definite	Moderate		
Creatinine	Normal	Count	18	32	30	10	90	
		% within Creatinine	20.0%	35.6%	33.3%	11.1%	100.0%	
		% within Cans Dysfunction	90.0%	88.9%	83.3%	100.0%	88.2%	
	Abnormal	Count	2	4	6	0	12	0.524
		% within Creatinine	16.7%	33.3%	50.0%	.0%	100.0%	
		% within Cans Dysfunction	10.0%	11.1%	16.7%	.0%	11.8%	
Total		Count	20	36	36	10	102	
		% within Creatinine	19.6%	35.3%	35.3%	9.8%	100.0%	
		% within Cans Dysfunction	100.0%	100.0%	100.0%	100.0%	100.0%	

CANS AND NEUROPATHY

NEUROPATHY	NORMAL		EARLY		DEFINITE		MODERATE	
	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES
ABSENT	11	6	9	13	2	15	3	1
PRESENT	1	2	9	5	11	8	3	3

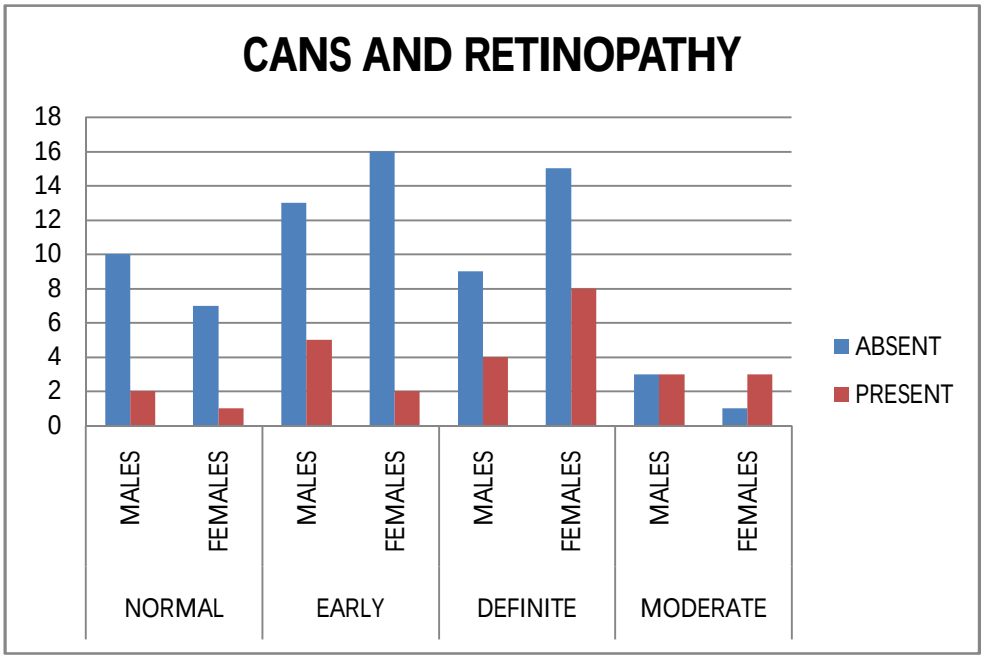


NEUROPATHY AND CANS

			Cans Dysfunction				Total	P value
			Normal	Early	Definite	Moderate		
Bioth	Present	Count	17	22	17	4	60	0.006
		% within Bioth	28.3%	36.7%	28.3%	6.7%	100.0%	
		% within Cans Dysfunction	85.0%	61.1%	47.2%	40.0%	58.8%	
	Absent	Count	3	14	19	6	42	
		% within Bioth	7.1%	33.3%	45.2%	14.3%	100.0%	
		% within Cans Dysfunction	15.0%	38.9%	52.8%	60.0%	41.2%	
Total		Count	20	36	36	10	102	
		% within Bioth	19.6%	35.3%	35.3%	9.8%	100.0%	
		% within Cans Dysfunction	100.0%	100.0%	100.0%	100.0%	100.0%	

CANS AND RETINOPATHY

RETINOPATHY	NORMAL		EARLY		DEFINITE		MODERATE	
	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES
ABSENT	10	7	13	16	9	15	3	1
PRESENT	2	1	5	2	4	8	3	3



RETINOPATHY AND CANS

			Cans Dysfunction				Total	P value
			Normal	Early	Definite	Moderate		
Fundus	Present	Count	17	29	24	4	74	0.034
		% within Fundus	23.0%	39.2%	32.4%	5.4%	100.0%	
		% within Cans Dysfunction	85.0%	80.6%	66.7%	40.0%	72.5%	
	Absent	Count	3	7	12	6	28	
		% within Fundus	10.7%	25.0%	42.9%	21.4%	100.0%	
		% within Cans Dysfunction	15.0%	19.4%	33.3%	60.0%	27.5%	
Total		Count	20	36	36	10	102	
		% within Fundus	19.6%	35.3%	35.3%	9.8%	100.0%	
		% within Cans Dysfunction	100.0%	100.0%	100.0%	100.0%	100.0%	

RESULTS

The present study comprised of 102 subjects of which 49 were males and 52 were females. A total of 82 (80.39%) were found to have CANS dysfunction of varying degrees. 75.7% males and 84.61% females were detected with CANS dysfunction.

Early CANS dysfunction was detected in 18 of 49 males (36.73%) and 17 of 52 females (32.69%). Definite CANS dysfunction was seen in 13 males (26.53%) and 21females (40.38%). Moderate CANS was detected in 6 males (12.2 %) and 4 females (7.69%).

When we compared age of patients with CANS function we found that in the age group of 31 to 40 years of 4 males 50% had normal CANS and 50% had CANS dysfunction. Of 12 females, 3 had (25%) normal CANS and 9(75%) had CANS dysfunction.

In 41to 50 years age group, of 13 males 6(46.15%) had no CANS dysfunction and 7(53.86%) had CANS dysfunction. Among the 13 females 2(15.38%) had normal CANS and 11(84.62%) had CANS dysfunction.

In 51 to 60 years age group, of the 20 males 2(10%) had normal CANS and 18(90%) had CANS dysfunction. Of 23 females 3(13.04%) has normal CANS and 20(86.96%) had CANS dysfunction.

In 61 to 70 years age group, of 12 males 2(16.66%) had normal CANS and 10(83.33%) had CANS dysfunction. All 5 females (100%) in this group had varying degrees of CANS dysfunction.

On comparing duration of diabetes with CANS dysfunction there were a total of 24 patients with less than 1 year of diabetes. Among these 6(25%) had normal CANS and 18(75%) had CANS dysfunction.

In the 30 subjects with duration of diabetes between 1 to 5 years 5(16.66%) had normal CANS and 25(83.33%) had CANS dysfunction.

In 6 to 10 years duration cohort we had 26 patients of which 4(15.38%) had normal CANS and 22(84.62%) had CANS dysfunction.

In 11 to 15 years diabetes duration group of a total of 13 patients, 4(30.76%) had normal CANS and 9(69.24%) had CANS dysfunction.

In the 9 patients with diabetes more than 15 years, 1(11.11%) had normal CANS whereas 8(88.89%) had CANS dysfunction.

A total of 27 patients had HbA1c of less than 7%. In this group with good glycaemic control, only 5 (18.51%) had normal CANS whereas 10 (37.03%) had early CANS, 9 (33.3%) had definite and 3 (11.11%) had moderate CANS dysfunction.

Among the 29 patients with HbA1c between 7.1 to 8 %, 7(24.13%) had normal CANS but 10 (34.48%) had early, 11(37.93%) definite and 1 (3.44%) had moderate CANS dysfunction.

In the cohort with 8.1 to 9 HbA1c there were 16 patients. Of these 2(12.2 %) had normal CANS, 6(36.5%) had early, 5(31.25%) had definite and 3(18.75%) had moderate CANS dysfunction.

In 9.1 to 10 HbA1c group of 11 patients 3(27.2%) had normal CANS, 3 (27.2%) early, 4 (36.36%) definite and 1 (9.09%) moderate CANS dysfunction.

19 patients had HbA1c > 10 %, of which 3 (15.78%) had normal CANS, 7(36.8%) early, 7(36.8%) definite and 2 (10.52%) moderate CANS dysfunction.

Diabetic nephropathy was detected in 17 patients who were enrolled in this study. Among the patients with nephropathy 15(88.23%) had CANS dysfunction. 85 patients were without nephropathy and CANS dysfunction was present in 67(78.8%)

60 patients had no neuropathy detected by biothesiometry. Of these 17(28.3%) had normal CANS and 43 (17.6%) had varied degrees of CANS dysfunction. A total of 42 patients were diagnosed with peripheral neuropathy of this 3 (7.1%) had normal CANS whereas 39(92.85%) had varying degrees of CANS dysfunction.

74 patients had no retinopathy. Among them 17 (22.9%) had normal CANS function whereas 57(77.02%) had some degree of CANS dysfunction. A total of 28 patients were diagnosed with different stages of retinopathy and in this cohort there were 3 (10.7%) with normal CANS and 25(89.28%) with varying degrees of CANS dysfunction.

CONCEPT OF P VALUE

- If the P value is 0.000 to 0.010 then significant at 1 level (highly significant)

- If the P value is 0.011 to 0.050 then significant at 5 level (significant)

- If the P value is 0.051 to 1.000 then not significant at 5 level (not significant)

DISCUSSION

In this present study the overall prevalence of CAN in the South Indian T2DM population was found to be 80.39%. Of this 34.31% had early CANS 33.33% had definite CANS and 9.80% had moderate CANS dysfunction. During history taking and physical examination all these patients who were included in the study were asymptomatic in relation to cardiac autonomic neuropathy.

Research done by Andrzej S.Krolewski who correlated CAN with retinopathy in type 1 DM found a strong correlation of CAN with diabetic retinopathy but diabetic nephropathy correlated weakly. Another study by Vincenza Spallone showed relationship between autonomic neuropathy, 24 hours BP profile and nephropathy in normotensive T1DM patients and DAN was significantly associated to increased urinary albumen excretion.

Basu et al from eastern India studied 50 patients with T2DM and their study revealed 54% prevalence and it was strongly associated with retinopathy and microalbuminuria.

Study by Elizabeth et al showed definite CANS dysfunction in 23% and early CANS dysfunction in 33%. No significant difference was found for gender and HbA1c but CAN was more common with older age, higher BP, nephropathy, neuropathy and retinopathy.

EURODIAB study found age, poor gylcaemic status, high systolic BP, neuropathy and retinopathy to be significant risk factors for CAN dysfunction.

Our study is unique as we have not only estimated the prevalence of cardiac autonomic neuropathy in T2DM population but also correlated it with diabetic neuropathy, nephropathy, retinopathy, HbA1c, age of patients, gender, and duration of diabetes.

In our study we found that CAN was not significantly associated with duration of diabetes, HbA1c and nephropathy.

There was almost equal distribution of the disease among both sexes. There was a significant association of CAN with increasing age, neuropathy, and retinopathy.

LIMITATIONS OF STUDY

- The cohort was not large enough to represent the whole population.

- A control group was not included in this study

- Nephropathy was diagnosed by urine PCR method.

CONCLUSIONS

- Cardiac autonomic neuropathy dysfunction appears much before patient manifest signs and symptoms of this disease.

- Hence CANS testing should be mandatory and started early to insist better metabolic control.

- As the problem is associated with other micro vascular complication, further deterioration should be prevented.

- Age has a significant association with cardiac autonomic neuropathy, hence elderly diabetic patients need regular CANS evaluation.

- CAN dysfunction is almost equal in prevalence among both the sexes.

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PROFORMA

PREVALANCE OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS AND ITS CORRELATION WITH OTHER MICROVASCULAR COMPLICATIONS

Name : Patient ID No:

Age/Sex : Contact No:

Occupation:

COMPLAINTS

☐ Postural giddiness

☐ Numbness of hands and feet

☐ Gustatory sweating

☐ Pins and needles sensation

☐ Palpitation

☐ Facial puffiness

☐ Bowel and bladder disturbances

☐ Decreased urine output

☐ Sexual dysfunction

☐ Peripheral edema

☐ Cotton wool sensation

☐ Blurring of vision

PAST HISTORY

☐ HT

☐ CAD

☐ Kidney disease

☐ STROKE/TIA

☐ Other Neurological disease

PERSONAL HISTORY

☐ Smoking

☐ Alcohol intake

GENERAL EXAMINATION

BP: Lying:

BP: Standing:

PULSE:

WEIGHT:

HEIGHT:

BMI:

SKIN:

SYSTEMIC EXAMINATION:

CVS:

RS:

P/A:

CNS:

INVESTIGATIONS

Blood Urea: mg/dl

Serum Creatinine: mg/dl

Plasma glucose-

Fasting: mg/dl

Postprandial: mg/dl

HbA1c: %

Urine PCR:

CAN analysis

Biothesiometry

Ophthalmic Fundus examination

ECG

PATIENT CONSENT FORM

Study Title	:	Prevalance of cardiac autonomic neuropathy in Type 2 Diabetes Mellitus and its correlation with other microvascular complications
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Name	:	
Age/Sex	:	
Identification Number	:	

Patient may check (☑) these boxes

The details of the study have been provided to me in writing and explained to me in my own language ❑

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ❑

I hereby consent to participate in this study. ❑

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological and biochemical tests. ❑

Signature/thumb impression

Patient's Name and Address:

Signature of Investigator

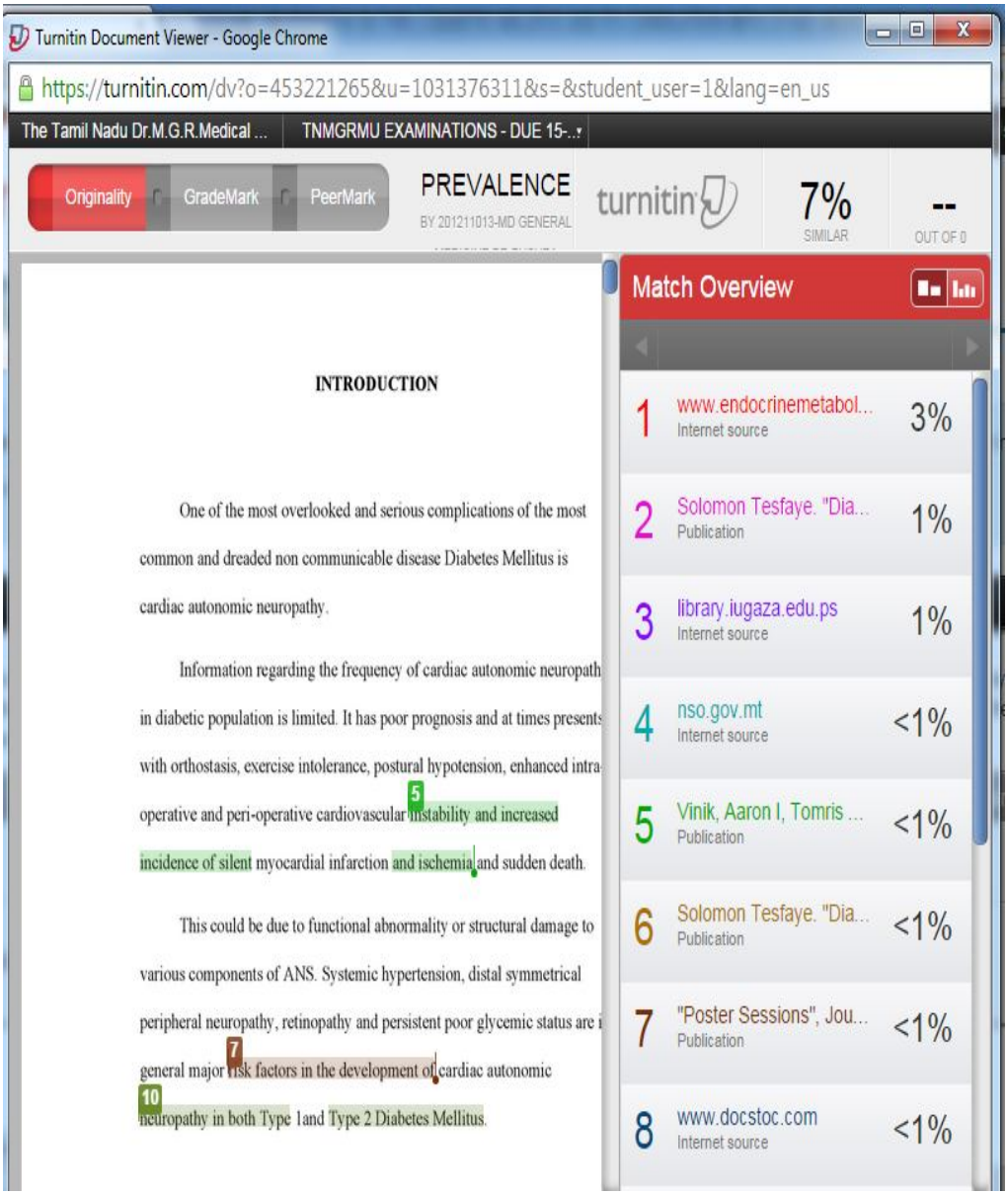
Study Investigator's Name:

S.No	AGE	SEX	Du	COM	PG	HBA1c	UPCR	UREA	Cr	BIOTH	FUNDUS	PARASYMPATHETIC	SYMPATHETIC	CANS DYSFUNCTION
1	61	F	10Y		119	6.4	0.03	18	1	MOD	NPDR	RHR GR II ST GR I	GR 0	EARLY CANS
2	44	F	6Y	HT	138	6.4	0.02	21	0.9	ML	N	NORMAL	NORMAL	NORMAL
3	45	M	4Y		236	12.3	0.02	16	0.7	N	N	STANDING GR II	GR 0	EARLY CANS
4	47	M	3Y	PSY ILL	270	12.6	0.02	22	1.2	N	N	STANDING GR II	GR 0	EARLY CANS
5	52	M	9 M		93	6.4	0.03	24	1.1	N	N	STANDING GR II	GR 0	EARLY CANS
6	38	F	7Y	HT	248	10.4	0.03	20	0.8	ML	N	STANDING GR II	GR 0	EARLY CANS
7	68	M	30Y	HT	182	8.3	0.44	44	1.4	MOD	NPDR	STANDING GR II	GR 0	EARLY CANS
8	57	M	3Y	HT	146	6.7	0.02	20	1.1	N	N	STANDING GR II	SHG GR I	EARLY CANS
9	55	F	3Y		207	10.3	0.03	18	0.9	N	N	DB GR II ST GR II	SHG GR I	DEFINITE CANS
10	33	F	1Y	HYP	231	8.8	0.02	34	1.2	N	N	GR 0	GR 0	NORMAL
11	66	M	N D		207	10.4	0.32	52	1.5	N	N		GR 0	NORMAL
12	40	F	N D	PSY ILL	178	6.9	0.03	22	1	N	N	DB GR I ST GR II	SHG GR II	DEFINITE CANS
13	59	F	7Y		291	9.2	0.02	18	1	N	N	NORMAL	GR 0	NORMAL
14	62	M	3Y	HT	72	4.9	1.4	52	3	ML	NPDR	STANDING GR II	SHG GR II	EARLY CANS
15	60	M	3Y		199	11.2	0.05	18	1	N	N	GR 0	GR 0	NORMAL
16	56	M	1Y		146	8.4	0.02	20	1.1	N	N	STANDING GR II	GR 0	EARLY CANS
17	51	F	6Y	HT CKD	114	6	0.64	45	2.1	ML	N	DB GRII ST GRII	SHG GR I	DEFINITE CANS
18	63	F	2Y		173	8.1	0.02	19	1	MOD	N	STANDING GR II	SHG GR II	DEFINITE CANS
19	67	M	6Y		118	7	0.03	20	1.1	ML	N	STANDING GR II	SHG GR II	DEFINITE CANS
20	56	F	11Y		76	6.2	0.04	20	0.9	N	NPDR	NORMAL	SHG GR II	EARLY CANS
21	55	F	N D		116	10.3	0.02	20	0.9	N	N	STANDING GR I	SHG GR II	EARLY CANS
22	54	M	10Y		136	9.9	0.7	20	1.1	SEV	NPDR	DB GR II ST GR II	SHG GR I	DEFINITE CANS
23	53	M	14Y	HT	164	7.5	0.02	24	0.9	MOD	NPDR	DB GRII RHR GRII ST GRII	SHG GR II	MODERATE CANS
24	56	M	N D		171	8	0.3	68	1.7	MOD	NPDR	DB GRI RHR GR II ST GRII	SHG GR I	EARLY CANS
25	54	F	6Y	HT	155	7.2	0.05	23	1.1	N	N	NORMAL	GR 0	NORMAL
26	70	M	7Y	HT	180	7.4	0.02	28	1.2	ML	N	DB GR II ST GR II	GR 0	DEFINITE CANS
27	49	F	6Y	HT Ca Cx	170	5.7	0.03	18	0.9	SEV	N	DB GR II ST GR II	SHG GR 0	DEFINITE CANS
28	49	M	4Y		206	8.2	0.03	18	1.2	N	N	STANDING GR II	SHG GR I	EARLY CANS
29	54	F	7Y	HT	88	5.4	0.42	40	1.8	ML	N	STANDING GR II	SHG GR I	EARLY CANS
30	35	F	4Y		144	9.4	0.03	18	1	N	N	STANDING GR II	SHG GR II	EARLY CANS

31	40	M	12Y		165	10.1	0.03	21	1	MOD	N	STANDING GR II	SHG GR II	EARLY CANS
32	43	F	14Y		130	7.8	0.03	18	0.8	MOD	NPDR	NORMAL	GR 0	NORMAL
33	52	M	8Y	HT	139	9.8	0.03	26	1.1	ML	N	STANDING GR II	SHG GR I	EARLY CANS
34	55	F	3Y	HT	92	5.8	0.02	20	0.9	ML	NPDR	DB GR II ST GR II	SHG GR II	MODERATE CANS
35	67	F	12Y	HT	220	11.1	0.28	33	1.3	N	N	DB GR II ST GR II	SHG GR II	MODERATE CANS
36	68	M	18Y		89	6.5	0.03	18	1	ML	NPDR	STANDING GR II	SHG GR II	DEFINITE CANS
37	32	M	3 M		102	5.7	0.03	18	1	N	N	RESTING GR II	SHG GR II	MODERATE CANS
38	45	F	3 M		130	8.2	0.03	25	1.1	N	N	RESTING HR II	SHG GR I	EARLY CANS
39	64	M	N D		146	7.9	0.02	20	1.1	ML	N	STANDING GR II	SHG GR II	DEFINITE CANS
40	61	M	10Y		106	5.7	0.13	18	1.2	ML	N	DB GR II ST GR II	SHG GR II	MODERATE CANS
41	56	F	8Y	HT	198	9	0.03	30	0.9	ML	N	STANDING GR II	SHG GR I	EARLY CANS
42	49	F	8Y		81	6.8	0.02	23	1	N	N	STANDING GR II	SHG GR I	EARLY CANS
43	58	F	7Y		258	14	0.1	26	1.2	ML	NPDR	DB GRII ST GR I	SHG GR I	DEFINITE CANS
44	38	F	2Y		238	9	0.02	22	0.9	N	N	STANDING GR II	SHG GR I	EARLY CANS
45	57	F	2Y		119	7.1	0.03	20	1	N	N	STANDING GR II	SHG GR II	DEFINITE CANS
46	60	F	16Y		181	8.3	0.04	28	1.1	SEV	NPDR	STANDING GR II	SHG GR II	DEFINITE CANS
47	59	M	17Y		352	6.4	0.03	18	1	MOD	NPDR	NORMAL	GR 0	NORMAL
48	55	F	4Y		147	8.2	0.5	44	1.4	N	NPDR	STANDING GR II	SHG GR II	DEFINITE CANS
49	57	F	12Y		207	10.4	0.03	25	1.2	N	NPDR	STANDING GR II	SHG GR II	DEFINITE CANS
50	58	F	4Y	HT	96	7	0.03	18	1	ML	N	STANDING GR II	SHG GR II	DEFINITE CANS
51	56	M	4Y		145	6.8	0.02	26	1	N	N	NORMAL	SHG GR II	EARLY CANS
52	55	F	5 M		153	7.4	0.04	17	0.7	N	N	RESTING HR GR II	SHG GR II	DEFINITE CANS
53	45	F	6Y		182	7.9	0.03	23	1.1	N	N	DB GR I	SHG GR II	EARLY CANS
54	37	F	N D		201	7.4	0.04	18	1.1	N	N	NORMAL	SHG GR II	EARLY CANS
55	47	F	5Y		76	6.9	0.09	22	1.1	ML	N	NORMAL	SHG GR II	EARLY CANS
56	55	F	2Y		436	10	0.04	22	1.2	N	N	STANDING GR II	SHG GR II	DEFINITE CANS
57	43	M	1Y		123	8.3	0.03	21	0.8	N	N	DEEP BREATHING GR II	SHG GR II	DEFINITE CANS
58	45	M	N D		184	7.8	0.05	23	0.9	N	N	NORMAL	SHG GR II	EARLY CANS
59	44	M	N D		208	8.2	0.03	23	1.1	N	N	NORMAL	GR 0	NORMAL
60	53	F	N D		130	5.4	0.02	34	1	N	N	NORMAL	GR 0	NORMAL
61	47	M	20Y		148	12.2	0.06	30	1.1	ML	NPDR	STANDING GR I	SHG GR I	EARLY CANS
62	37	M	1 M		110	7.2	0.04	23	1	N	N	NORMAL	GR 0	NORMAL

63	52	M	7Y	HT	230	8.4	0.04	19	1.1	ML	NPDR	DB GR II RHR GR II ST GRII	SHG GR II	MODERATE CANS
64	57	M	10Y	HT	121	6.2	0.34	49	1.6	MOD	NPDR	STANDING GR II	SHG GR II	DEFINITE CANS
65	60	F	13Y		185	10.9	0.02	26	1	N	N	NORMAL	SHG GR II	EARLY CANS
66	47	F	N D		182	8.9	0.03	23	1.1	N	N	STANDING GR II	SHG GR II	DEFINITE CANS
67	40	F	N D		153	7.5	0.04	17	0.9	N	N	STANDING GR I	SHG GR II	EARLY CANS
68	58	M	2Y		304	10.3	1.12	57	2.4	ML	NPDR	STANDING GR II	SHG GR II	DEFINITE CANS
69	54	F	8Y	HT HYP	149	12.2	0.6	48	2	N	NPDR	STANDING GR II	SHG GR II	DEFINITE CANS
70	59	M	N D	HT	385	14	0.03	26	1.2	MOD	N	STANDING GR II	SHG GR II	DEFINITE CANS
71	50	F	N D		145	8	0.02	26	1	N	N	STANDING GR II	SHG GR II	DEFINITE CANS
72	38	F	8Y		130	7.4	0.02	34	1	N	N	STANDING GR II	SHG GR II	DEFINITE CANS
73	68	M	2Y		184	10.2	0.54	42	1.9	N	NPDR	NORMAL	NORMAL	NORMAL
74	40	F	1Y		174	9.7	0.04	21	1.1	N	N	STANDING GR II	SHG GR II	DEFINITE CANS
75	51	M	7Y	HT	138	6.5	0.03	21	1.1	ML	N	STANDING GR I	SHG GR II	EARLY CANS
76	50	F	1Y	HT	127	7.4	0.04	18	0.6	MOD	N	STANDING GR II	SHG GR II	DEFINITE CANS
77	50	F	7Y	HT	209	8	0.04	22	1	N	N	NORMAL	SHG GR II	EARLY CANS
78	50	F	3 M	HT	148	7.8	0.6	28	0.8	N	N	STANDING GR I	SHG GR II	EARLY CANS
79	30	F	2 M		207	9.8	0.06	20	0.8	N	N	NORMAL	GR 0	NORMAL
80	51	M	4Y		85	7	0.04	38	1.3	MOD	N	DEEP BREATHING GR II	SHG GR II	DEFINITE CANS
81	60	F	12 Y	HT	229	13.3	0.1	27	1.1	N	NPDR	DB GR II RHR GR II	SHG GR 0	DEFINITE CANS
82	52	F	16Y		184	9.9	0.01	18	1	N	NPDR	STANDING GR II	SHG GR II	DEFINITE CANS
83	63	M	1Y		149	8.7	0.04	19	1.1	N	N	DB GR II ST GR II	SHG GR II	MODERATE CANS
84	32	F	2Y	HT HYP	232	9.4	0.04	24	1.2	N	N	STANDING GR II	GR 0	EARLY CANS
85	55	M	N D		132	7.2	0.03	27	1.2	N	N	NORMAL	SHG GR II	EARLY CANS
86	57	M	N D	HT	192	8	0.04	22	0.8	N	N	STANDING GR II	SHG GR II	DEFINITE CANS
87	40	F	3Y		89	5.4	0.02	18	0.6	N	N	NORMAL	GR 0	NORMAL
88	45	F	3Y		131	6.8	0.02	23	1	N	N	STANDING GR II	SHG GR II	DEFINITE CANS
89	43	M	6Y		159	7.2	0.04	29	1.2	ML	N	STANDING GR II	GR 0	EARLY CANS
90	70	M	N D		249	8	0.03	22	1.2	ML	PDR	STANDING GR I	SHG GR II	EARLY CANS
91	60	F	16Y		207	7.6	0.26	42	1.4	SEV	NPDR	STANDING GR II	SHG GR II	DEFINITE CANS
92	63	M	11Y	HT	134	8	0.06	20	1.1	ML	N	STANDING GR II	SHG GR II	DEFINITE CANS
93	65	F	12Y	HT HYP	168	9.2	0.08	24	1.2	MOD	NPDR	DB GR II ST GR II	SHG GR II	MODERATE CANS
94	50	M	13Y		188	9.9	0.12	27	1.2	N	N	NORMAL	GR 0	NORMAL

95	68	F	17Y		269	12.8	0.4	42	1.3	ML	NPDR	DB GR II ST GR II	SHG GR II	MODERATE CANS
96	32	M	3Y		127	7.1	0.02	18	0.7	N	N	NORMAL	GR 0	NORMAL
97	41	M	12Y		141	7.6	0.03	20	1	N	N	NORMAL	GR 0	NORMAL
98	55	M	7Y		172	8.8	0.3	36	1.2	N	NPDR	DB GR II ST GR II	SHG GR II	MODERATE CANS
99	60	M	18Y	HT	144	7.8	0.06	28	1.1	MOD	N	STANDING GR II	SHG GR II	DEFINITE CANS
100	50	M	11Y	HT	131	7.4	0.04	24	1	N	N	NORMAL	GR 0	NORMAL
101	49	M	4Y		122	6.4	0.03	18	0.8	N	N	NORMAL	GR 0	NORMAL
102	42	M	6Y		174	7.8	0.04	20	0.9	N	N	NORMAL	GR 0	NORMAL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INTRODUCTION
One of the most overlooked and serious complications of the most common and dreaded non communicable disease Diabetes Mellitus is cardiac autonomic neuropathy.
Information regarding the frequency of cardiac autonomic neuropath in diabetic population is limited. It has poor prognosis and at times presents with orthostasis, exercise intolerance, postural hypotension, enhanced intra-operative and peri-operative cardiovascular instability and increased incidence of silent myocardial infarction and ischemia and sudden death.
This could be due to functional abnormality or structural damage to various components of ANS. Systemic hypertension, distal symmetrical peripheral neuropathy, retinopathy and persistent poor glycemic status are i general major risk factors in the development of cardiac autonomic neuropathy in both Type 1and Type 2 Diabetes Mellitus.
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INTRODUCTION

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. Pushpa Masiwal,
Post Graduate,
Institute of General Medicine,
Madras Medical College,
Chennai – 600003.

Dear Pushpa Masiwal,

The Institutional Ethics Committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled **"Prevalence of cardiac autonomic neuropathy in Type-2 Diabetes Mellitus and its correlation with other microvascular complications"** No.10062014

The following members of Ethics Committee were present in the meeting held on 03.06.2014 conducted at Madras Medical College, Chennai-3.

1.	Dr. C. Rajendran, M.D.	-- Chairperson
2.	Dr. R. Vimala, M.D., Dean, MMC, Ch-3.	-- Deputy Chair Person
3.	Prof. Kalaiselvi, MD., Vice-Principal, MMC, Ch-3	-- Member
4.	Prof. Nandhini, M.D. Inst. of Pharmacology, MMC, Ch-3.	-- Member
5.	Dr. G. Muralidharan, Director Incharge , Inst. of Surgery	-- Member
6.	Prof. Md Ali, MD., DM., Prof & HOD of MGE, MMC, Ch-3.	-- Member
7.	Prof. Ramadevi, Director i/c, Biochemistry, MMC,Ch-3.	-- Member
8.	Prof. Saraswathy, MD., Director, Pathology, MMC, Ch-3.	-- Member
9.	Prof. Tito, Director, i/c. Inst. of Internal Medicine, MMC	-- Member
10.	Thiru. Rameshkumar, Administrative Officer	-- Lay Person
11.	Thiru. S. Govindasamy, BABL, High Court, Chennai-1.	-- Lawyer
12.	Tmt. Arnold Saulina, MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Vice-Principal
Madras Medical College
Chennai-600 003.

Member Secretary, Ethics Committee